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# PHYSIOLOGICAL EFFECTS OF RADIATION

## I. A STUDY OF THE *IN VITRO* EFFECT OF HIGH FEVER TEMPERATURES UPON CERTAIN EXPERIMENTAL ANIMAL TUMORS*†

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THIS is the first of a series of studies upon the effects of heat and roentgen radiation both alone and in combination, and with various dosage systems, upon normal tissues and various types of tumors. In order to simplify some of the conditions, this investigation was begun by employing *in vitro* methods, recognizing that certain limitations would be present in the application of the data obtained. The relative magnitudes of time and temperatures obtained may not correspond directly to results which might be obtained *in vivo*. The method would appear to be capable of yielding information of fundamental importance, chiefly concerning the general trends of destructive effects of fever temperatures upon tumor tissues of several types in different species under similar experimental conditions.

Various workers have studied the effect of heating surviving, transplantable tumor cells *in vitro*, but they tested the effect of temperatures greater than those tolerated by the living human body, and under only very simple experimental conditions. Rohdenburg and Prime[12] found that temperatures between 42.0 and 46.0° C. were lethal *in vitro* to the tumor cells of mouse sarcoma 180 within relatively short exposure periods, namely, 30 to 180 minutes. These temperatures, however, are above the practical physiological limits of the febrile range.

It has been the experience in this clinic that a rectal temperature of 41.5° C. in the human subject is the highest temperature which is safe for long periods (six to twenty-four hours—Warren[9]). While rectal temperatures of 42.0° C. have been tolerated for an hour or slightly more without evident damage, the condition of the patient is such as to suggest that a longer period at this temperature would result in irreparable damage to the human organism if it did not result immediately in a fatality. A study of the range of temperature maxima in laboratory animals suggests that a similar critical level is present in them also. In fact, the common laboratory animals are not able to tolerate as long a period with the rectal temperature at 41.5° C. as is the human subject. A study of temperature gradients (unpublished) indicates that the rectal temperature is only a rough average, some parts of the body (liver, kidney, and brain) being from 0.2 to 0.5° C. higher and some lower (subcutaneous and superficial structures). Thus with a rectal temperature

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of 41.5° C., the temperature in some organs may rise as high as 42.0° C.

The *in vitro* technique reported in this communication was designed to parallel the normal physiological environment as much as possible in order to establish some basis for the use of fever temperatures as a possible method for selectively killing these malignant cells without damage to the host. Temperatures below 41.5° C. have little destructive effect upon the tumor cell, 41.5° C. being the lowest energy level showing this effect within a reasonable time period. A temperature of 42.0° C., (43.0° C. in the rabbit experiment) was used by us mainly to show the destructive effects more strikingly, and to spread the data over several temperatures (37.0 to 42.0° C.) in order to study the difference in rate and limits of lethal effect with small changes in temperature.

### A. MOUSE SARCOMA 180

A moderate-sized, rapidly growing tumor was excised from a single host for each experiment and the translucent portions cut up with a razor blade into slices 0.3 to 0.5 mm. in thickness. These slices were then cut up into fragments measuring approximately 6 to 15 sq. mm., which were placed in 100 or 200 cc. Erlenmeyer flasks containing freshly filtered (Berkefeld N) Locke's solution of high phosphate buffer and glucose content (Dickens and Šimer[3]). From 3 to 7 cc. of the Locke's solution was allowed per tumor fragment, depending upon the duration of the heating. The flasks were flushed out with oxygen, stoppered, and placed in the shaking apparatus in the various constant temperature water baths ranging from 37.0 to 42.0° C. (±0.002° C.) previously described (Bishop, Carpenter, and Warren[1]). Water baths were found to be superior to air incubators for many reasons. No good air incubator for the purpose could be found, the chief defect being the tremendous temperature gradients in the stock incubators. These gradients were not completely removed by stirring the air with fans. Close control of the temperature was difficult. The low specific heat of air makes it impracticable to obtain a quick elevation of temperature in the flask, Petri dish, or test tube containing the tumor fragments. In many cases, in the air incubator, a 200 cc. flask containing 100 cc. of Locke's solution may not reach 41.5° C. (from room temperature of 26.0° C.) under an hour's time. In the water bath, without shaking, thermocouple measurements show this rise to occur within fifteen minutes to 41.4° C., and an additional five minute period for the last 0.1° C. With shaking, this total time is reduced to approximately five minutes so that no appreciable error in the allotted time of exposure is introduced.

The Locke's solution was adjusted to a pH of 7.4 for all of the experiments. The pH of the solution containing the tumor fragments was measured after the heat exposures by the colorimetric method in several of the experiments. The pH usually dropped to 7.0 or 7.1 and rarely lower than 6.9 with the longest exposures, and usually reached about 7.1 in the shorter ones. The control specimens at 37.0° C. showed changes in the pH approximately similar to those at the higher temperatures. This degree of lowering of the pH appeared to have no effect upon the take characteristics of the controls as compared to those of the stocks.

Bacterial contamination was tested by inoculating Douglas' broth medium with samples of the tumor fragments and Locke's solution. A slight degree of contamination was frequently found, a motile coccobacillus being the chief offender. These few bacteria did not appear to influence the taking ability of the control fragments at 37.0° C., nor of the fragments heated at the higher temperatures, as compared to the taking of the stock tumors which also were contaminated by similar but fewer bacteria. In three of the nineteen experiments, abscesses appeared at the site of tumor inoculation in some of the animals. These experiments were discarded.

The flasks were shaken at a rate of about 80 to 100 oscillations per minute. The excursion of the shaking was about 5 cm. The degree of shaking was guided by previous observations (Jares[4]) so that maximum oxygen consumption by the cells was evident from microrespirometer experiments conducted at the higher fever temperatures. This was true even at the end of the longer exposures when the oxygen consumption of the cells reached a very low rate as a result of the heating.

Besides those fragments placed in the water bath at 37.0° C., additional controls were afforded by the inoculation of untreated fragments of the same tumor used in the experi-

ment into animals which then served as stock tumor animals.

The tumor fragments were removed from the water baths after allotted periods of time, and immediately inoculated subcutaneously into the inguinal region of healthy mice. Each experiment included a total of 60 to 150 mice which were divided into groups each containing 5 to 25—usually 10—for each temperature and period. All animals were of the same sex (female) and of approximately the same age (young, adult), and were fed with Purina Dog Chow throughout.

The animals were examined at weekly intervals and measurement of the tumor growth was made with the usual caliper and outline method. The experiments were done over a period of two years (July 29, 1932 to August 27, 1934), through different seasons of the year to rule out successively, seasonal variation, stock variation, and tumor generation variation. Tumor was obtained from two sources* neither of which showed any deviation from the usual, well-known characteristics. In addition to observing the incidence of takes, the growth characteristics were observed on each animal as represented by the latent period (from inoculation to first definite palpatory evidence of tumor), the actively growing period of the tumor (from the first definite palpatory evidence of tumor until exitus of the host), and the survival period (from inoculation to exitus as a result of the tumor growth) of the host.

In an occasional experiment, spontaneous regression of the tumor occurred in a few cases in the stocks, controls, and heated fragments after an initial growth period. This was more common in the heated group. Such regressing tumors usually grew to a comparatively small size. Ulceration, although occasionally present, was not necessarily a factor in the regression of these relatively few instances.

Histological study of the inoculated areas at several intervals shortly after inoculation was done at the various temperatures and durations of heating.

## RESULTS

It is obvious that the results obtained in a study such as this depend, to a large extent, upon the technique and methods employed, but if these be consistent throughout, the results at different temperatures may be compared. In the experiments reported here—after some orienting preliminary experiments—every attempt was made to keep the technique constant throughout so that the data might be of comparative value, both between the different temperatures and the various tumor generations.

Sixteen separate experiments were undertaken. The first five of these (Table 1) are to be regarded as preliminary ones, in which several refinements in the technique were evolved. Their value here is to demonstrate the advantages of an improved technique over the simple one usually employed in this type of research. The chief criterion used to show these advantages was the percentage of takes obtained at the various heating periods and the duration of heating at which no takes occurred.

In these earlier trials, the tumor slices were a little thicker than in the last eleven experiments; test tubes instead of flasks were used as containers, and the amount of Locke's solution per fragment was several times smaller; the pH of the solution reached a lower level; the fragments were not shaken during the heating period. The control fragment in these five preliminary experiments was usually inoculated into the same animal on the side opposite to that of the fragment heated at the higher temperatures, and while this procedure appeared to be satisfactory for the testing of a take, some of the growth characteristics, such as the rapidity of growth and the host's survival period, might suffer as a result of the increased demands upon the host by the two tumors. This practice was thus discontinued and only a single fragment was inoculated into each animal, in the subsequent experiments.

The portion of the fifth experiment in which shaking was introduced is shown in Chart 1. It can be seen that the fragments shaken during the heat exposure took in a

* This tumor material was kindly supplied us by Dr. J. B. Murphy of the Rockefeller Institute, and by Dr. J. W. Schereschewsky of the Office of the Cancer Investigations, United States Public Health Service, Harvard Medical School.

much higher percentage of cases than the unshaken did, probably due to the more adequate gaseous diffusion and interchange between the cells and the surrounding fluid medium which occurs under these conditions. The average results of these five groups. The thermal death time is also much longer which is probably another indication of better technique. In the above charts and tables, except Table 1, are shown only the results obtained under the best

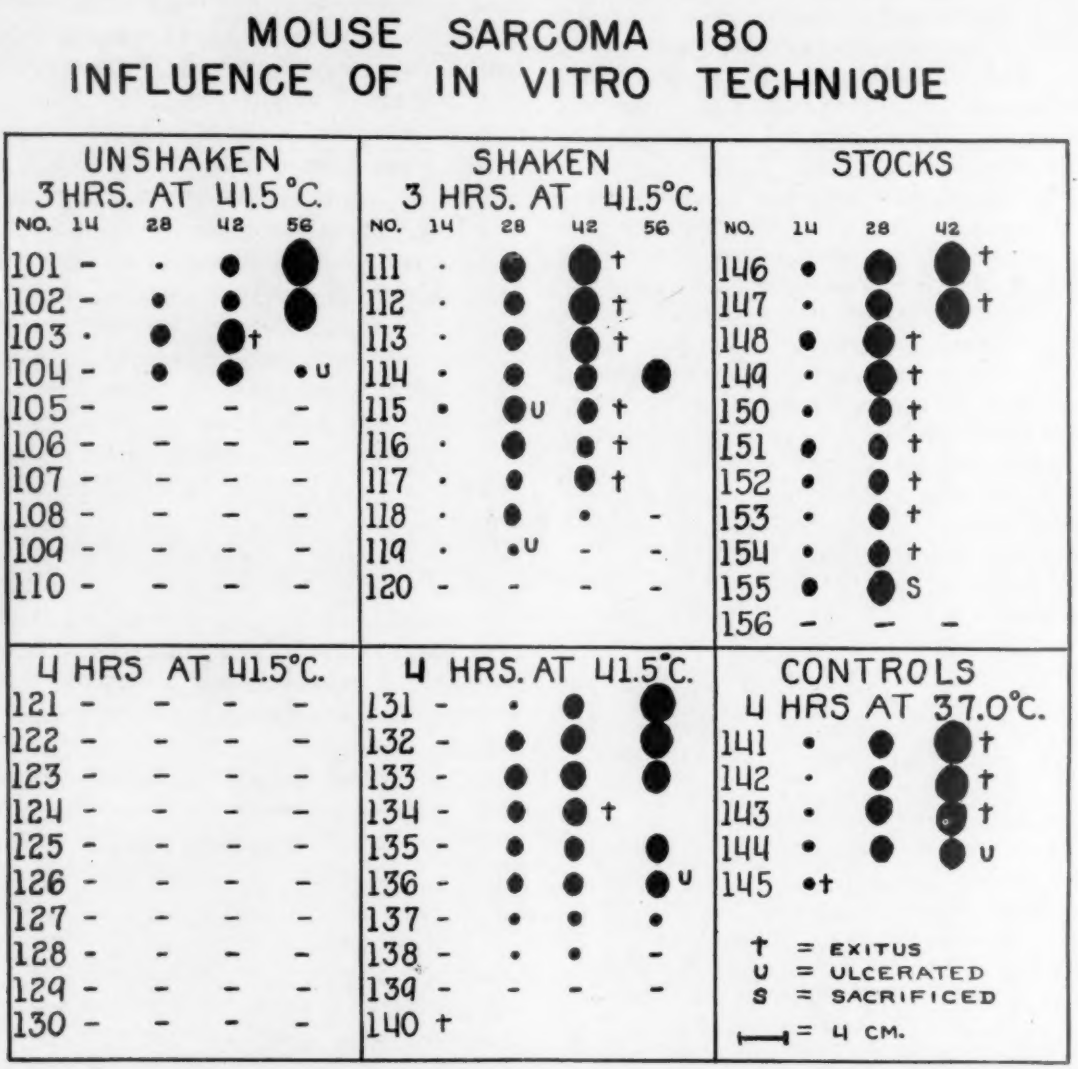


CHART. 1. Experiment No. 5 showing the improved effect resulting from shaking the tumor fragments during the period of heating upon the incidence of takes after inoculation.

preliminary experiments (unshaken fragments) are recorded in Table 1, and the results of the improved technique in Table 11. On comparison between Tables 1 and 11, it is evident that the percentage of takes and the limits of viability at similar heating periods are much greater and more consistent in the groups in which the fragments were kept in motion than in the unshaken

conditions, i.e. large volumes of Locke's solution, continuous shaking, and a very thin slice of tumor tissue transplanted into a single site per animal, as described above under "Method."

*Controls at 37.0° C.* In the control series of animals (Table 11 and Chart 11) when the total of 87 inoculations is surveyed for

TABLE I

EFFECT OF IN VITRO HEATING UPON VIABILITY OF MOUSE SARCOMA 180
TOTALS AND AVERAGES OF THE FIVE PRELIMINARY EXPERIMENTS

Fragments Unshaken—Preliminary Experiments

| Stocks | | | Hours Heated | Tumor fragments heated in constant temperature water bath | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 37.0° C. | | | 40.0° C. | | | 41.0° C. | | | 41.5° C. | | | 42.0° C. | | |
| No. Inoc. | No. Takes | % Takes | | No. Inoc. | No. Takes | % Takes | No. Inoc. | No. Takes | % Takes | No. Inoc. | No. Takes | % Takes | No. Inoc. | No. Takes | % Takes | No. Inoc. | No. Takes | % Takes |
| 47 | 43 | 91.5 | | | | | | | | | | | | | | | | |
| | | | 2–5 | 59 | 55 | 93 | | | | | | | | | | | | |
| | | | 3 | | | | | | | | | | 12 | 4 | 33 | 2 | 0 | 0 |
| | | | 4 | | | | | | | | | | 12 | 0 | 0 | 2 | 0 | 0 |
| | | | 5 | | | | | | | 2 | 1 | 50 | 22 | 0 | 0 | 2 | 0 | 0 |
| | | | 6 | | | | | | | 2 | 0 | 0 | 50 | 2 | 6.7 | | | |
| | | | 7 | | | | 2 | 2 | 100 | 2 | 0 | 0 | | | | | | |
| | | | 8 | | | | | | | 4 | 3 | 75 | 4 | 0 | 0 | | | |
| | | | 9 | | | | 2 | 1 | 50 | | | | | | | | | |
| | | | 10 | | | | | | | 5 | 2 | 40 | 5 | 0 | 0 | | | |
| 47 | 43 | 91.5 | | 59 | 55 | 93 | 4 | | | 15 | | | 85 | | | 6 | | |

the periods of heating between five and twenty hours, the average percentage of takes is 94.1 per cent as compared with 96.2 per cent for the stocks. This is very good agreement considering the trauma to which the tumor cells are exposed under the conditions of the experiment. It indicates as well as anything could that the *in vitro* results obtained at higher temperatures are due to the temperature elevation rather than a time-trauma factor.

In the 78 cases analyzed for *latent period* over the same exposure periods at 37.0° C., the average variation is between 5 and 9.8

TABLE II

EFFECTS OF IN VITRO HEATING UPON VIABILITY OF MOUSE SARCOMA 180
TOTALS AND AVERAGES OF ELEVEN EXPERIMENTS

Fragments Shaken—Improved Technique

| Stocks | | | Hours Heated | Tumor fragments heated in constant temperature water bath | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 37.0° C. | | | 40.0° C. | | | 41.0° C. | | | 41.5° C. | | | 42.0° C. | | |
| No. Inoc. | No. Takes | % Takes | | No. Inoc. | No. Takes | % Takes | No. Inoc. | No. Takes | % Takes | No. Inoc. | No. Takes | % Takes | No. Inoc. | No. Takes | % Takes | No. Inoc. | No. Takes | % Takes |
| 132 | 127 | 96.2 | 1 | | | | | | | | | | 8 | 7 | 88 | 9 | 9 | 100 |
| | | | 2 | | | | | | | | | | 9 | 8 | 89 | 10 | 10 | 100 |
| | | | 3 | | | | | | | | | | 14 | 13 | 93 | 8 | 2 | 25 |
| | | | 4 | 5 | 5 | 100 | | | | 5 | 5 | 100 | 30 | 27 | 90 | 10 | 4 | 40 |
| | | | 5 | | | | | | | 5 | 5 | 100 | 25 | 20 | 80 | 17 | 4 | 24 |
| | | | 6 | 19 | 18 | 94.7 | | | | 4 | 3 | 75 | 23 | 17 | 74 | 21 | 2 | 9.5 |
| | | | 7 | | | | | | | | | | 10 | 9 | 90 | 37 | 2 | 5.4 |
| | | | 8 | | | | 4 | 4 | 100 | | | | 20 | 14 | 70 | 37 | 0 | 0 |
| | | | 9 | 10 | 10 | 100 | 5 | 5 | 100 | 10 | 10 | 100 | 18 | 7 | 38.8 | 15 | 0 | 0 |
| | | | 10 | 15 | 14 | 93.3 | 4 | 4 | 100 | | | | 32 | 9 | 28 | | | |
| | | | 11 | | | | | | | | | | 33 | 11 | 33.3 | | | |
| | | | 12 | 7 | 6 | 86 | | | | | | | 51 | 20 | 39.2 | | | |
| | | | 13 | 5 | 5 | 100 | | | | | | | 47 | 9 | 19.1 | | | |
| | | | 14 | 5 | 5 | 100 | | | | | | | 26 | 2 | 7.7 | | | |
| | | | 15 | 11 | 10 | 91 | | | | | | | 15 | 0 | 0 | | | |
| | | | 16 | 5 | 4 | 80 | | | | | | | 19 | 0 | 0 | | | |
| | | | 18 | | | | | | | | | | 10 | 0 | 0 | | | |
| | | | 20 | 5 | 5 | 100 | | | | | | | 10 | 0 | 0 | | | |
| 132 | 127 | 96.2 | | 87 | 82 | 94.1 | 13 | | | 24 | | | 400 | 173 | | 164 | 32 | |

days with the average at 7.2 days. The greatest spread (see Chart II) was at ten and fifteen hours, although in the five inoculations at twenty hours the spread is only between five and eight days. The spread of the latent period of the stocks was between three and twelve days with the average at 5.8 days (50 cases).

making it impracticable to determine a satisfactory end point. The cases chosen were only those in which the most evident cause of exitus was the tumor. For the controls this period (Tables III and IV) averaged 32.8 days (twenty-two and forty-two days) in 51 cases analyzed. For the stocks this averaged 32.0 days (25 cases).

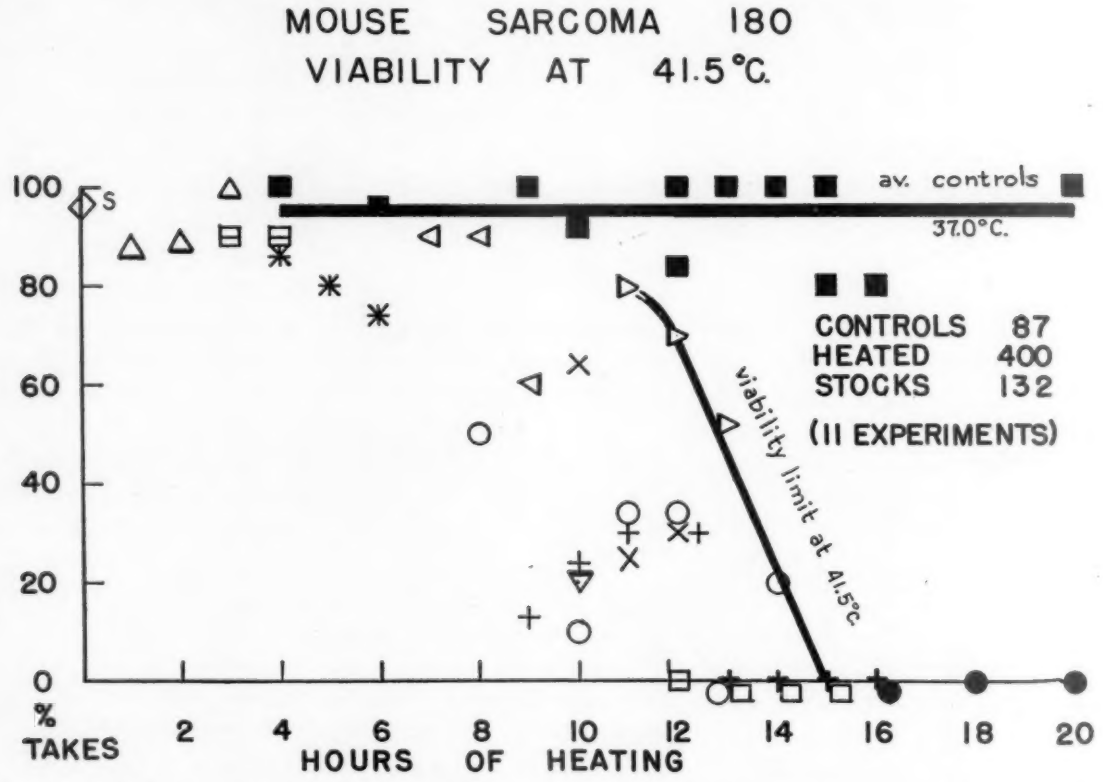


CHART II. Percentage of takes after various periods of heating of the tumor fragments at 41.5° C. Each point represents a group of 5 to 25 animals. Each experiment is indicated by a separate symbol. The control group at 37.0° C. for each experiment was run for the longest period of heating at the higher temperature.

The period of actively growing tumor (from the first palpatory evidence of tumor to the exitus of the host from the cachexia produced by the growing tumor mass) is probably a better indication of permanent damage to the tumor than is the length of life of the animal after inoculation because of the variability in the latent period shown in the specimens heated at fever temperatures. The numbers analyzed are smaller in some instances because ulceration of the tumor or intercurrent infection caused exitus before the natural span of life, thus

*40.0 to 41.0° C.* In the first experiments with the improved technique, several sets of fragments were exposed to these temperature ranges with no apparent effect upon the percentage of takes (Table II) and with only a slight effect noted in the latent period (Table III) and the actively growing period (Table IV). Since the thermal death time at 41.5° C. was quite long (fifteen hours) it did not seem practical to extend this part of the investigation further.

*Effects at 41.5° C.* It can be seen from Chart II and Table II that a band or range

TABLE III

AVERAGE LATENT PERIOD—MOUSE SARCOMA 180

Stocks Average 5.8 Days (50 Cases)
Summary of Eleven Experiments

| Temperature | Hours in Bath | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 20 | General Average |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 37.0° C. | Days | | | | 8.0 | | 6.1 | | | 7.7 | 9.0 | | 6.8 | 6.4 | 6.0 | 9.8 | 5 | 6.7 | 7.2 |
| | Cases | | | | 5 | | 18 | | | 9 | 12 | | 6 | 5 | 5 | 9 | 4 | 5 | 78 |
| 40.0° C. | Days | | | | | | | | 7.8 | 10 | 10 | | | | | | | | 9.3 |
| | Cases | | | | | | | | 4 | 5 | 4 | | | | | | | | 13 |
| 41.0° C. | Days | | | | 13 | 9.8 | 13 | | | 9.1 | | | | | | | | | 11.2 |
| | Cases | | | | 5 | 5 | 4 | | | 10 | | | | | | | | | 24 |
| 41.5° C. | Days | 7.6 | 11.4 | 7.5 | 10.1 | 10.0 | 10.6 | 14.1 | 13.9 | 14.5 | 18.7 | 17.1 | 15.7 | 15.1 | 22.5 | | | | 13.8 |
| | Cases | 7 | 7 | 13 | 18 | 20 | 17 | 9 | 13 | 7 | 9 | 10 | 22 | 9 | 2 | | | | 163 |
| 42.0° C. | Days | 8.4 | 7.5 | 14.5 | 17.7 | 14.8 | 14.0 | 16.5 | | | | | | | | | | | 13.3 |
| | Cases | 9 | 10 | 2 | 3 | 4 | 2 | 2 | | | | | | | | | | | 32 |

of lethal exposure times (twelve to fifteen hours) of the heated tumor fragments was obtained, indicating some variation from experiment to experiment and also within the same experiment. The limit of viability is shown by the heavy sloping line in Chart II. There is a gradual decrease in the percentage of takes in the various experiments during the first eleven hours of the exposure to 41.5° C. There is a much more rapid decline in the number of takes between ten and fourteen hours as the proximity of the thermal death time is approached. None of the fragments was able to produce a viable tumor after fifteen hours of exposure to 41.5° C. This is taken to be the approximate thermal death time for this tumor with this technique at this temperature. In contrast, the controls showed a high incidence of takes even after twenty hours of exposure at 37.0° C.

The longer the heat exposure, the longer the *latent period* became (Table III and Chart III). The tumors (after four hours or more of exposure) appeared in some cases as late as twenty or twenty-five days after

TABLE IV

ACTIVELY GROWING PERIOD—MOUSE SARCOMA 180

Stock Average 32 Days (25 Cases)

| Temperature | Hours in Bath | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 20 | General Average |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 37.0° C. | Days | | | | 32.3 | | 36 | | | 37 | 22.1 | | 42.6 | 30 | 26.5 | 37.5 | 42.0 | 22.5 | 32.8 |
| | Cases | | | | 4 | | 6 | | | 4 | 10 | | 6 | 3 | 4 | 6 | 4 | 4 | 51 |
| 40.0° C. | Days | | | | | | | | 42.3 | 32.8 | 32.7 | | | | | | | | 35.9 |
| | Cases | | | | | | | | 4 | 5 | 3 | | | | | | | | 12 |
| 41.0° C. | Days | | | | 37.3 | 41 | 30.5 | | | 31.3 | | | | | | | | | 35 |
| | Cases | | | | 3 | 4 | 2 | | | 7 | | | | | | | | | 16 |
| 41.5° C. | Days | 30 | 30.5 | 33.2 | 36.4 | 36 | 37.7 | 38 | 37.5 | 38.8 | 31.1 | 33 | 30.1 | 27.6 | 42.5 | | | | 34.4 |
| | Cases | 6 | 8 | 4 | 10 | 11 | 14 | 4 | 10 | 5 | 8 | 4 | 14 | 3 | 2 | | | | 103 |
| 42.0° C. | Days | 33 | 30 | 23 | 33 | 35 | 31 | 35 | | | | | | | | | | | 31.4 |
| | Cases | 8 | 9 | 1 | 4 | 3 | 1 | 2 | | | | | | | | | | | 28 |

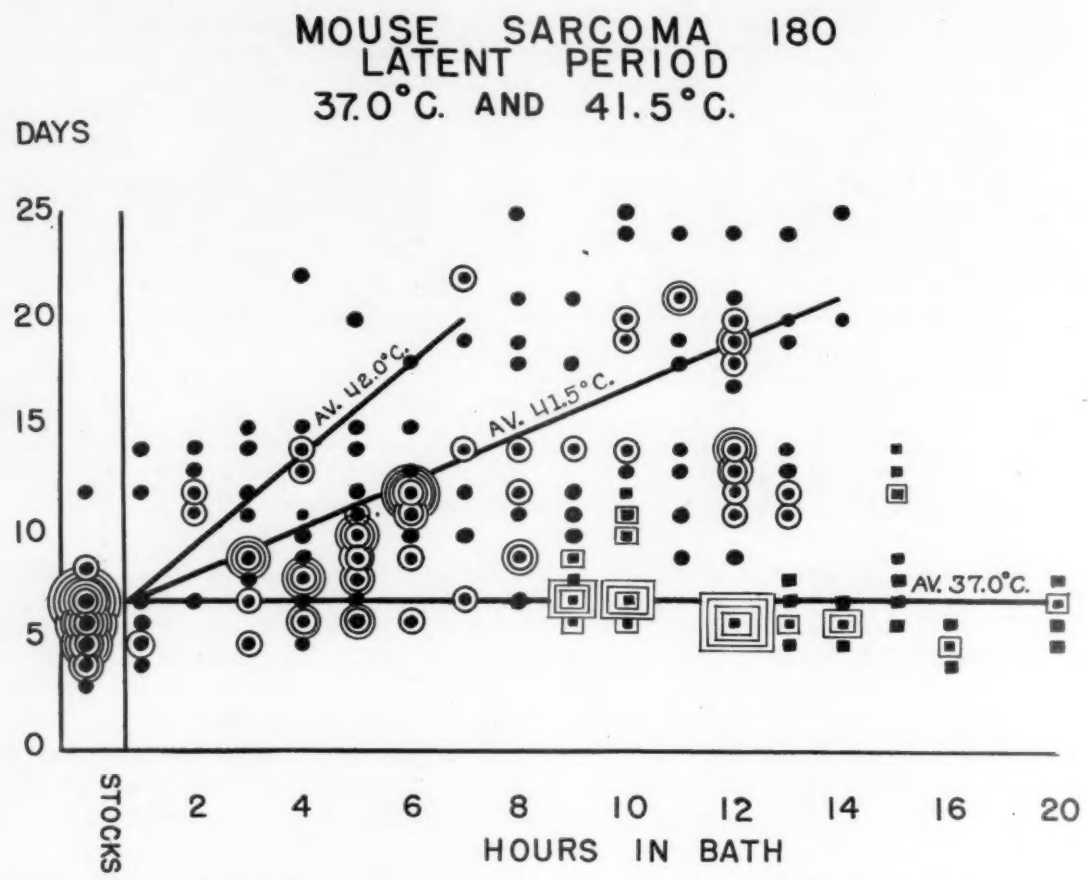


CHART III. The period from inoculation to first palpatory evidence of tumor is taken as the latent period. Each point represents the latent period of an individual animal. The controls at 37.0° C. are indicated by squares. All of the round points show the values obtained by heating at 41.5° C. for the various hours. The results of the exposure to 42.0° C. are not plotted but their average is indicated by the upper oblique line.

inoculation instead of in the usual five to seven days in the stocks and controls. The proportion of rapidly growing tumors tended to decrease slightly with the prolongation of the heating (Chart IV). The survival period of the tumor bearers rapidly increased after inoculation of the fragments which were heated from one to nine hours, after which this characteristic became quite irregular. This increase is due to the lengthening of the latent period (Charts III and IV). The spread of the *actively growing period* at 41.5° C. is illustrated in Chart IV and Table IV. While the spread is rather wide, the average for all the tumors originating from fragments heated for various times is 34.4 days (103 cases) in comparison to the stock average of thirty-two days (25 cases) and the control average of 32.8 days (51 cases). This seems to suggest that once the surviving tumor cells start to grow they grow at about the normal rate (Chart IV). This may be contrasted with the increase in latent period with increasing exposure indicated by the slope of the *average latent period* line for 41.5° C. shown in Chart III. Here the injury to the cells is indicated by a delay in the appearance of a palpable tumor mass. That this is not due entirely to the technique is illustrated by the short latent period and the unchanged actively growing period of the controls maintained at 37.0° C. for twenty hours (latent period five to eight days; actively growing period nineteen to thirty-one days).

*Effect of 42.0° C.* This temperature produced a narrower range of lethal exposure times (six to eight hours) of the tumor fragments than did the temperature of 41.5° C. (Chart v). The slope of the *limit of viability* is much steeper, and the approximate thermal death time is eight hours, or about half that at 41.5° C. (fifteen hours).

As with the 41.5° C. experiment, the *latent period* increases progressively but at a faster rate with the increase in the time of heating. The slope of the 42.0° C. average line in Chart III shows this increased damaging effect. Some cells evidently survive which grow feebly at first. This damage is further indicated by the low incidence of takes as the length of exposure approached the thermal death time. The *actively growing* period (average 31.4 days) is approximately the same on the whole as that for 41.5° C. (34.4 days) and the control (32.8 days—see Table IV). A difference of a few days in this long period apparently is of no significance. The survival period is little changed as is indicated by the sums of the latent period (Table III) and the actively growing period (Table IV).

*Histological Studies.* In several of the experiments, the initial number of animals inoculated was increased so that a few fragments at each temperature and duration of heating could be observed at various intervals after inoculation.

Examination of the inoculation site of the heated implants and their surrounding

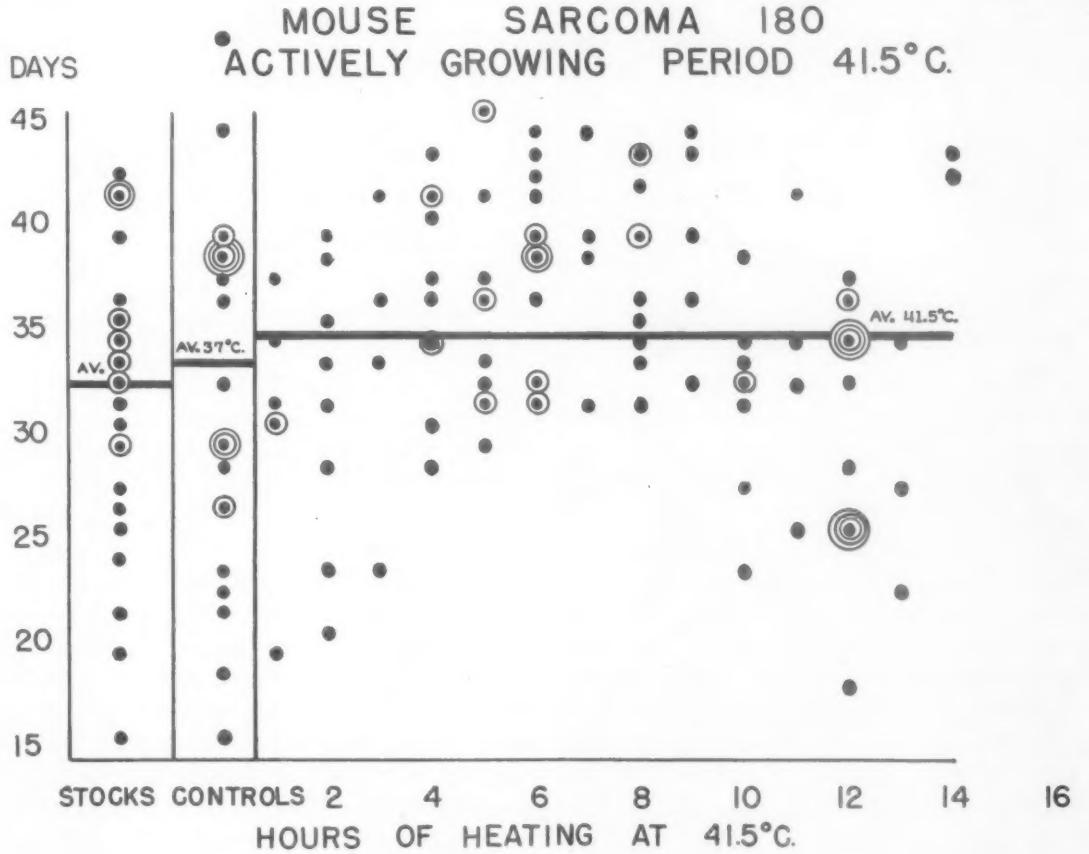


Chart IV. If the latent period is subtracted from the survival period, the actively growing period is obtained. Cases of static or ulcerated tumor growth were eliminated from this analysis. It is evident that there is no difference in the actively growing period among the stocks, controls maintained at 37.0° C., or the fragments maintained at 41.5° C., as shown by the spread and the averages (heavy lines). Each point represents an individual animal. The results at 42.0° C. were so similar that they are not indicated.

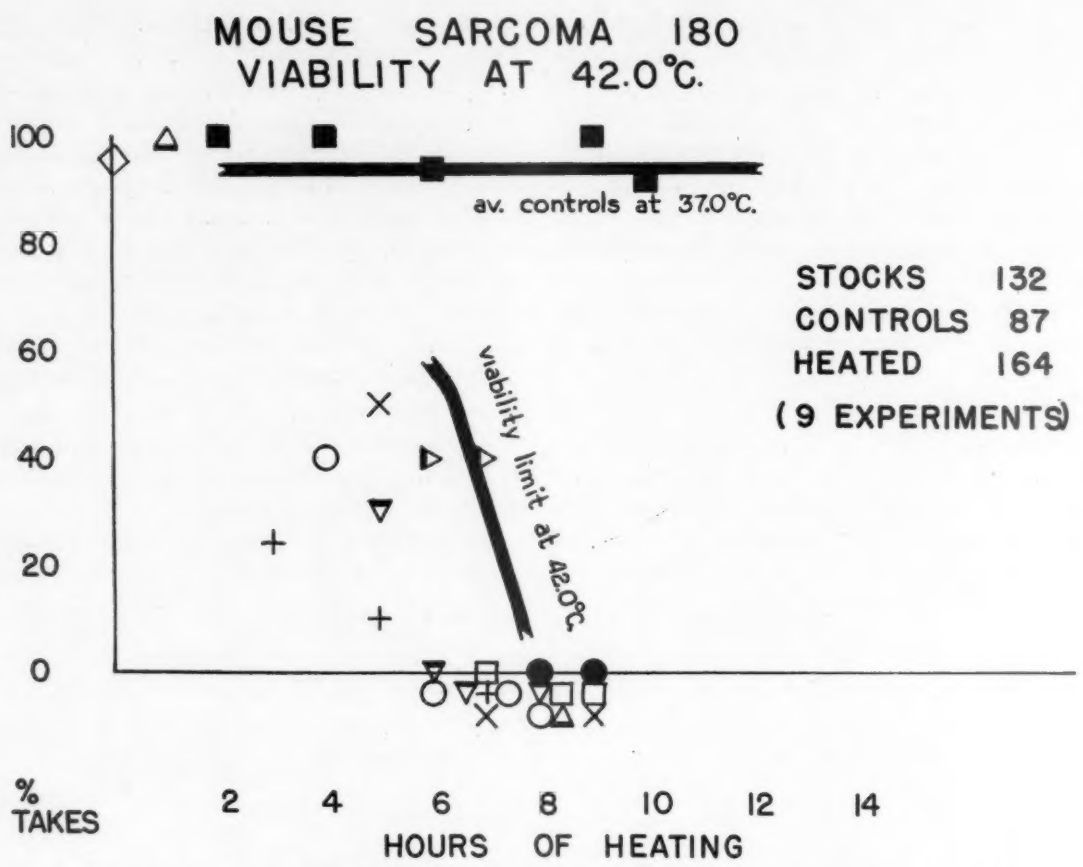


CHART V. The incidence of takes after various periods of heating of the tumor fragments at 42.0° C. Each symbol represents a separate experiment, as in Chart II. Similar symbols in Chart II and this chart represent trials within the same experiment.

tissues two days after inoculation showed some polymorphonuclear and round cell infiltration about the implant which was usually separated from adjacent tissue by a narrow, empty space. The implant generally presented more marked central cellular damage than peripheral. The nuclei of the tumor cells were usually quite pale with the routine hematoxylin and eosin stain. The cytoplasm was somewhat granular, and disintegrated, or absent in many cases, leaving the nuclei bare. The closer the heat exposure approached the thermal death time, the more marked were these evidences of injury to the cells. Mitosis was conspicuously absent. The controls at 37.0° C. showed the same type of change but to a lesser degree.

The three-day-old inoculation sites presented a picture similar to the two-day-old sites except that only a very few polymorphonuclear and round cells were seen. In some cases exposed below the thermal death time, the tumor cells exhibited less marked destruction, probably indicating beginning recovery.

The four-day-old sites still showed tumor cells with pale nuclei and indistinct cytoplasm, but in general the cells did not appear to be as much disturbed as those examined in the earlier stages of disintegration and recovery. Occasional mitotic figures were seen in those cases where the heat exposures were not long enough to prevent some takes in the respective groups. The controls showed frequent mitotic figures and cellular growth at this stage.

At six days, histological study of the implants heated less than the respective

thermal death times, and the controls disclosed marked mitotic activity and growth. Eight- and twelve-day specimens showed further mitotic activity and growth.

Implants treated for a time period in the neighborhood of the thermal death time at each temperature (where companion fragments did not take) and those heated beyond the thermal death time for the particular experiment, showed only cellular debris when removed from the animals at various periods after inoculation.

On comparison of the implants kept at 37.0° C. with those kept at 41.5 and 42.0° C. for the experimental periods, the specific effects of the higher temperatures were apparent histologically a few days after inoculation. There was no histological difference in the specific effects of 41.5 and 42.0° C. other than the time factor. In general, the injury was in proportion to the length of heating at the given temperature.

Although it has been previously observed (Woglom[10,11]), it may be of some corroborative value to mention parenthetically here that the inoculation of the heat-treated tumor cells which failed to take did not confer upon these mice any noticeable refractoriness to subsequent inoculation with normal tumor. Mice Numbers 121 through 130, shown in Chart 1, were inoculated with heated tumor fragments which failed to take. Fifty-six days after inoculation with these heated fragments, implantation with normal stock tumor resulted in characteristic, rapidly growing tumors in these 10 mice. Inoculation with stock tumor at various intervals (both

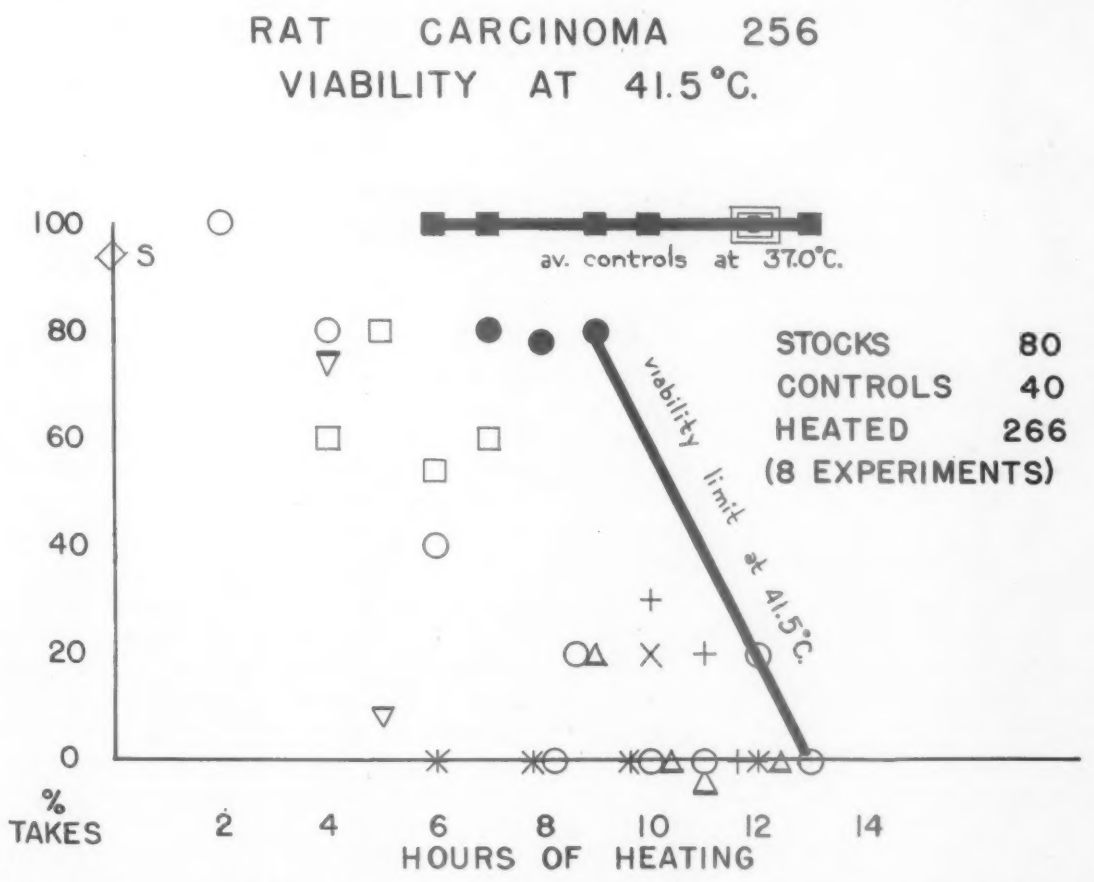


Chart vi. Percentage of takes after various periods of heating of the tumor fragments at 41.5° C. Each experiment is indicated by a separate symbol. Each point represents an average of from 5 to 15 animals. The control groups were exposed at 37.0° C. for the longest period of each experiment at 41.5° C.

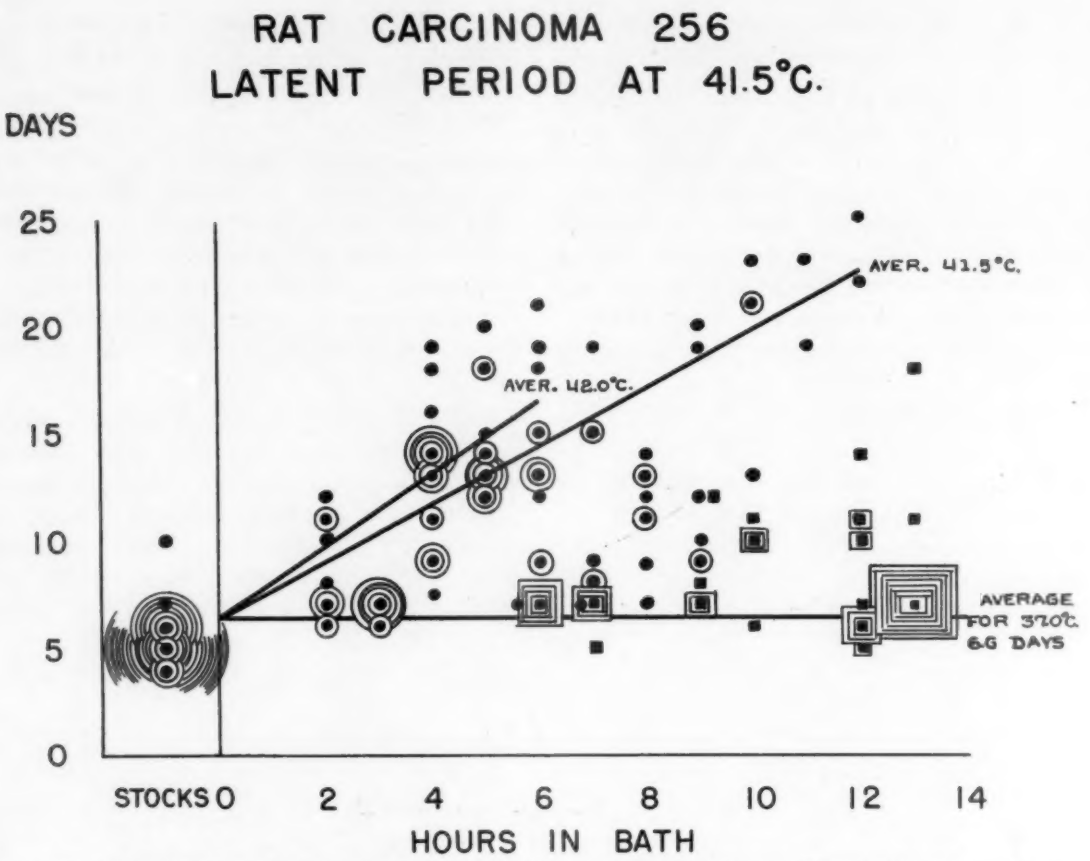


CHART VII. The latent period represents the period between inoculation and first palpatory evidence of tumor. Each point represents an individual case. The squares show the spread of the controls at 37.0° C. The round points show the spread of the latent periods of the fragments exposed to 41.5° C. Their average is shown by the longer heavy line. Only the average for those exposed at 42.0° C. is shown, i.e. the upper, shorter heavy line.

longer and shorter than the above fifty-six day period) after the implantation of the heat-killed fragment uniformly resulted in the usual rapid growth of the transplant (25 cases).

### B. RAT CARCINOMA 256*

(with the technical assistance of Johanna Walther, R. N.)

#### METHOD

The technique and procedure employed here have been fully described above in dealing with mouse tumor 180. The rats used were bred in our colony and their usual response to the inoculation of this rat tumor has been consistent for several years. Young adult animals weighing from 50 to 110 grams were selected for inoculation. They were maintained under similar conditions of housing, diet, room temperature, etc.

Eight experiments were undertaken, extending over a period from December, 1932, to June, 1934, thereby controlling tumor virulence variation, possible seasonal and stock deviation, and other variable factors in the hosts and tumor generations. Each experiment included from 50 to 170 animals indicated by a common symbol in Charts VI and VIII. For each heating period these total numbers were divided into groups of 10 animals, although occasionally this number varied between 5 and 15 animals, the average for each group being represented by a single point on Charts VI and VIII. The animals were inoculated with fragments heated while shaken in highly buffered Locke's solution at a given temperature for the indicated periods of time. Approximately 600 rats were employed in this investigation.

* Obtained through the courtesy of Dr. F. C. Wood, Director of the Institute for Cancer Research, Columbia University.

In one of the experiments, an additional control procedure was introduced: one-half of the tumor fragments at each temperature and heating period was oxygenated and stirred without shaking by continuous and rapid bubbling of oxygen through the Locke's solution during the heating procedure; the other half was shaken in the usual manner. No significant difference was noted in the percentage of tumor takes so that this refinement was not included in the remaining experiments.

Measurements of the pH of the Locke's solution at the conclusion of the various heating periods at the different temperatures produced results very similar to those obtained with the mouse 180 tumors. For the longer periods, the pH usually descended to about 6.9. The shorter periods of heating affected the pH to a lesser degree, the readings ranging from 7.0 to 7.2. The lowest value observed was 6.7. This occurred in an experiment showing bacterial contamination and in which all of the pH values in the flasks were lower than usual.

Bacterial contamination was not a troublesome factor in these experiments. Inoculation of Douglas' broth medium with samples from some of the flasks containing the heated tumor fragments revealed diphtheroids and cocci. In some of the experiments, cultures made from the flasks showed no bacterial contamination.

## RESULTS

*Effects of 41.5° C.* A range of *survival times* was observed for each of the various experiments. Failure of every fragment to take (thermal death time) was found to

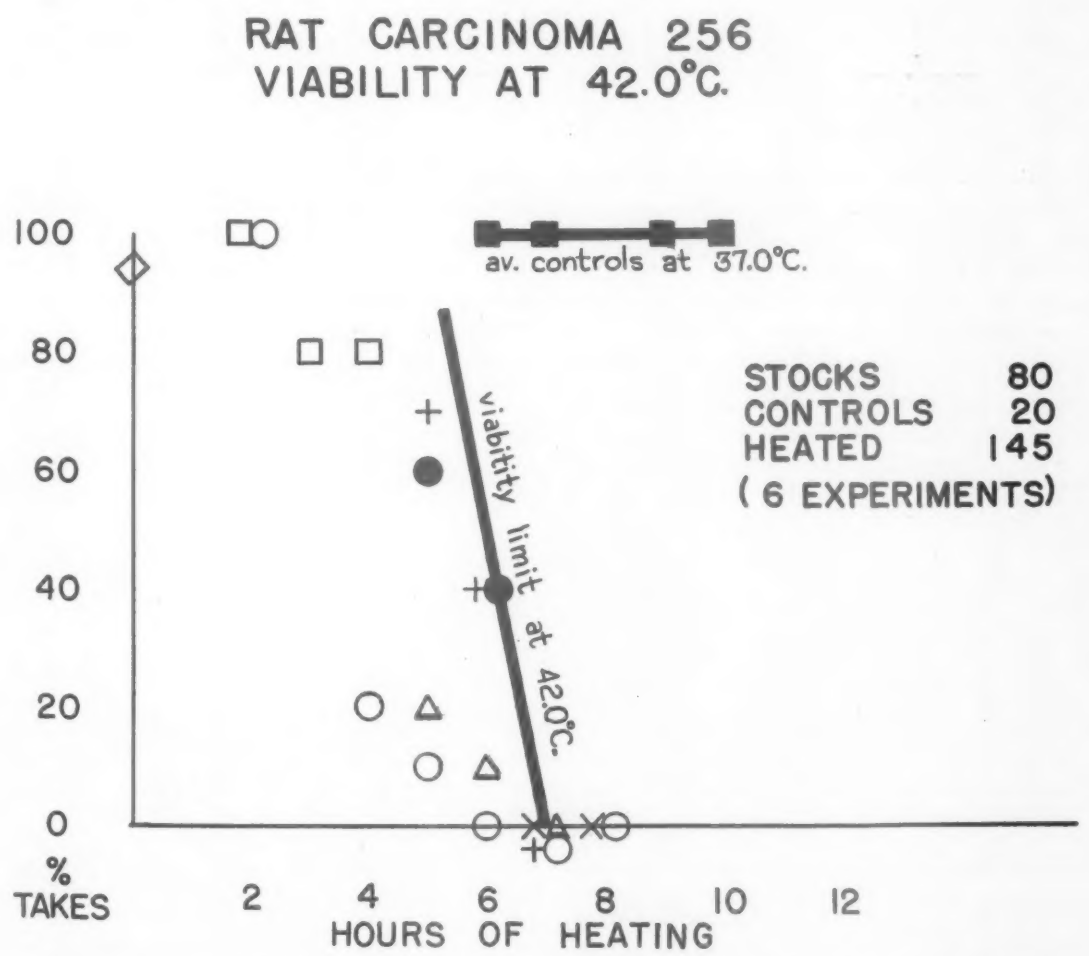


Chart VIII. The percentage of takes of tumor fragments exposed to 42.0° C. Each symbol represents a single experiment as in Chart I, and where they are identical, this represents trials at both temperatures of the same tumor material.

TABLE V

EFFECT OF IN VITRO HEATING UPON THE VIABILITY OF RAT CARCINOMA 256

Totals and Averages of Eight Experiments

| Stocks | | | Hours Heated | Tumor Fragments Heated in Constant Temperature Water Bath | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 37.0° C. | | | 41.5° C. | | | 42.0° C. | | |
| No. Inoc. | No. Takes | % Inoc. | | No. Inoc. | No. Takes | % Takes | No. Inoc. | No. Takes | % Takes | No. Inoc. | No. Takes | % Takes |
| 6 | 5 | 83.4 | 2 | | | | 10 | 10 | 100 | 15 | 15 | 100 |
| 4 | 4 | 100 | 3 | | | | 9 | 7 | 77.8 | 5 | 4 | 80 |
| 5 | 5 | 100 | 4 | | | | 23 | 17 | 74 | 15 | 6 | 40 |
| 5 | 5 | 100 | 5 | | | | 25 | 13 | 52 | 30 | 12 | 40 |
| 9 | 8 | 89 | 6 | 5 | 5 | 100 | 30 | 12 | 40 | 35 | 7 | 20 |
| | | | 7 | 5 | 5 | 100 | 10 | 7 | 70 | 30 | 0 | 0 |
| | | | 8 | | | | 24 | 8 | 33.3 | 15 | 0 | 0 |
| | | | 9 | 5 | 5 | 100 | 20 | 6 | 30 | | | |
| | | | 10 | 5 | 5 | 100 | 37 | 4 | 10.8 | | | |
| | | | 11 | | | | 39 | 3 | 7.7 | | | |
| | | | 12 | 12 | 12 | 100 | 29 | 2 | 6.9 | | | |
| | | | 13 | 10 | 10 | 100 | 10 | 0 | 0 | | | |
| 29 | 27 | 93.1 | | 42 | 42 | 100 | 266 | 89 | | 145 | 44 | |

vary in the different experiments between six hours and thirteen hours of heating at 41.5° C. The approximate thermal death time at this temperature was thus thirteen hours. Chart VI and Table V represent a summary of the average percentages of takes for the individual experiments. The *latent period* increased quite progressively with the increased duration of the treatment of the tumor fragments (Chart II and Table II). The slope of the average line resembles that obtained from mouse sarcoma 180. The survival period followed a similar trend, as is indicated by the sums of the average latent periods and average actively growing periods summarized in Tables VI and VII. The *actively growing period*, as with the mouse tumor 180, was not influenced to any extent (Table VII).

*Effect of 42.0° C.* Chart VIII shows that the decrease in the percentage of takes as the heating period increases was quite

TABLE VI

RAT CARCINOMA 256

AVERAGE LATENT PERIODS EIGHT EXPERIMENTS

Stock Average = 5.5 days (27 cases)

| Temperature | Hours | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | Average | Limits of Variation Days |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 37.0° C. | Days | | | | | 7 | 6.6 | | 8.2 | 9.4 | | 8.1 | 8.5 | 6.6 | 5 to 18 |
| | Cases | | | | | 5 | 5 | | 5 | 5 | | 12 | 10 | 42 | |
| 41.5° C. | Days | 8.8 | 6.7 | 21.9 | 14.4 | 13.7 | 11.6 | 11.4 | 13.2 | 19.5 | 24.3 | 23.5 | | | 6 to 31 |
| | Cases | 10 | 7 | 17 | 13 | 12 | 7 | 8 | 6 | 4 | 3 | 2 | 0 | 89 | |
| 42.0° C. | Days | 10 | 9.8 | 15.2 | 12.5 | 16.3 | | | | | | | | | |
| | Cases | 15 | 4 | 6 | 12 | 7 | | | | | | | | 44 | 7 to 23 |

TABLE VII

RAT CARCINOMA 256

AVERAGE ACTIVELY GROWING PERIODS EIGHT EXPERIMENTS

Stocks average = 39.0 days (21 cases)

| Temperature | Hours | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | Average | Limits of Variation Days |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 37.0° C. | Days | | | | | | 36.7 | | 40.5 | 40 | | 39.6 | 47.5 | 40.8 | 30 to 44 |
| | Cases | | | | | | 3 | | 4 | 2 | | 9 | 4 | 22 | |
| 41.5° C. | Days | 48.6 | 36.4 | 45.0 | 36.6 | 43.9 | 41.5 | 39.5 | 43.5 | 49.7 | 47.0 | 56.5 | | 44.4 | 25 to 71 |
| | Cases | 6 | 2 | 8 | 5 | 8 | 4 | 4 | 4 | 3 | 2 | 2 | | 48 | |
| 42.0° C. | Days | 39.4 | 32 | 40.7 | 48.6 | 50.0 | | | | | | | | 42.1 | 28 to 64 |
| | Cases | 8 | 1 | 3 | 10 | 4 | | | | | | | | 26 | |

sharp. The approximate thermal death time was seven hours.

The latent period (Chart VII and Table VI) was lengthened slightly more rapidly than with the heating at 41.5° C. This is indicated by the average line for 42.0° C. in Chart VII. This did not change quite as fast as it did with the mouse tumor 180. The actively growing period was not affected.

C. JENSEN RAT SARCOMA

This group of experiments upon the Jensen rat sarcoma is reported for brevity in tabular form. The procedure was essentially the same as that of the preliminary experiments reported in Section A of this series. These were the first exploratory experiments in this entire study (1932). Later refinements of technique were not used. The fragments were not shaken dur-

TABLE VIII

JENSEN RAT SARCOMA

Incidence of Takes and Average Latent Period (no shaking of tumor fragments)

| Hours Heated | 37.5° C. | | | | 39.0° C. | | | | 40.0° C. | | | | 41.0° C. | | | | 41.5° C. | | | | 42.0° C. | | | | 43.0° C. | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. Inoc. | No. Takes | % Takes | Av. Latent Period | No. Inoc. | No. Takes | % Takes | Av. Latent Period | No. Inoc. | No. Takes | % Takes | Av. Latent Period | No. Inoc. | No. Takes | % Takes | Av. Latent Period | No. Inoc. | No. Takes | % Takes | Av. Latent Period | No. Inoc. | No. Takes | % Takes | Av. Latent Period | No. Inoc. | No. Takes | % Takes | Av. Latent Period |
| 1 | 1 | 0 | 0 | | | | | | | | | | | | | | | | | | 2 | 0 | 0 | | | | | |
| 2 | 2 | 2 | 100 | 7 | | | | | | | | | | | | | 2 | 2 | 100 | 7 | 2 | 2 | 100 | 9 | | | | |
| 3 | 2 | 2 | 100 | 7 | | | | | | | | | | | | | 2 | 2 | 100 | 7 | 2 | 2 | 100 | 12 | | | | |
| 4 | 2 | 2 | 100 | 6 | | | | | | | | | | | | | 2 | 2 | 100 | 12 | 2 | 0 | 0 | | | | | |
| 5 | 2 | 2 | 100 | 6 | | | | | | | | | 2 | 1 | 50 | 7 | 2 | 1 | 50 | 10 | | | | | | | | |
| 6 | 14 | 13 | 93 | 5.5 | 4 | 3 | 75 | 6 | 4 | 2 | 50 | 8 | 6 | 5 | 83 | 9 | 6 | 5 | 83 | 10 | 4 | 0 | 0 | | 4 | 0 | 0 | |
| 7 | 2 | 2 | 100 | 7 | | | | | | | | | 2 | 2 | 100 | 12 | 2 | 0 | 0 | | | | | | | | | |
| 8 | 2 | 1 | 50 | 9 | | | | | | | | | 2 | 1 | 50 | 10 | 2 | 0 | 0 | | | | | | | | | |
| 9 | 2 | 2 | 100 | 12 | | | | | | | | | 2 | 2 | 100 | 9 | 2 | 0 | 0 | 0 | | | | | | | | |
| 10 | 12 | 11 | 92 | 5.3 | 4 | 3 | 75 | 7 | 4 | 2 | 50 | 6 | 6 | 2 | 33 | 13 | 6 | 1 | 17 | 33 | 4 | 0 | 0 | | | | | |
| Totals Aver- | 41 | 37 | 90.3 | 6.0 | 8 | | | | 8 | | | | 20 | | | | 26 | | | | 16 | | | | 4 | | | |

Summary of tumor takes and latent periods at the various temperatures and durations of exposures. The flasks containing the tumor fragments were not shaken during the exposures. The latent period values are averages for the recorded numbers of takes.

ing the exposures and two heated fragments and a control fragment were inoculated into the majority of the rats. The data are recorded here only because they illustrate the same biological response to fever temperatures as shown by rat tumor 256.

The end point of viability (thermal death time) was not thoroughly investigated, although ten hours at 41.5° C. and four hours at 42.0° C. approximate the shortest range of viability. With the other tumors, the maximum range of viability was considered to be the thermal death time. Further work was not done with this tumor because it spontaneously regressed frequently in our stocks, and other tumors were found to be more suitable.

Table VIII summarizes the results obtained. It is noteworthy that the percentage of tumor takes in stock animals averaged about 60 per cent over a period of a year and a half, whereas the average percentage in the controls at 37.5° C. was 90.3 (41 cases).

### D. BROWN-PEARCE RABBIT EPITHELIOMA

The Brown-Pearce rabbit epithelioma is much more rapidly growing than the mouse and rat tumors, and has many of the characteristics of malignant human tumors. Its high percentage of takes (98 per cent in 384 animals by the fragment method), regular growth characteristics, relatively high percentage of metastases, the short period between inoculation and exitus of the animal (averaging forty-five days in those having metastases) and the low percentage of spontaneous regressions (less than 1 per cent) make it a suitable tumor for our purposes of investigation.

#### METHOD

In general, this experiment has been conducted in the same manner as reported for the mouse and rat experiments except that the temperatures used were somewhat higher. These experiments extended over a period of almost two years (1933–1934) in order to increase the number of animals used and to exclude as much as possible seasonal, stock, and tumor generation variations.

The rabbits were young, adult males with well-developed testes and in good condition, purchased through our regular breeder. Several breeds were used.

Pearce and Brown[6] observed that the rabbit's testis was the most favorable site for growth of this epithelioma. In addition, the testis is a very convenient location for palpation and measurement of the tumor. Therefore, tumor suspensions were inoculated into the central portions of the testes after exposure to various fever temperatures for different durations. After four such experiments (see Chart IX) the *fragment method* of inoculation was employed in subsequent trials since it was found upon tests in our stocks that this method offered several marked advantages over the suspension method: (1) higher incidence of takes (98 as compared to 83 per cent); (2) slightly faster appearance time (5.6 compared to 7.5 days); (3) much more definite initial palpatory evidence of the tumor since the origin of growth started from a small, circumscribed focus rather than from a diffuse infiltration of cells around the injection site; (4) fewer extensions up the testicular cord and less frequent generalized metastases; (5) much more definite and uniform volume changes instead of a sudden change from a vague infiltration to a relatively large mass within a day or two; (6) a longer thermal death time probably indicating an improvement in the *in vitro* conditions of the experiment (less mechanical damage, more constant volume of tumor cells, diminished chances of infection, etc.).

The *suspension* of tumor was made up in buffered Locke's solution. Young, growing portions of tumor were selected, cut up with scissors, ground with mortar and pestle, and strained through gauze. From 0.50 to 1.0 cc. of the resulting material was injected with a No. 18 needle.

For the *fragment* technique young, solid, growing portions of the tumor were cut with a razor blade into slices about 0.5 mm. thick, then cut up into rectangular pieces (4.0 to 6.0 mm. × 2.0 to 3.0 mm.) which would slip easily into a sterile No. 12 trocar. A single fragment was injected into the center of the testis. The fragments did not break up even after being shaken in the flasks in the water baths at 37.0 or 42.0° C. for thirty-five hours, although some cells were loosened and became detached at the periphery of the fragment.

As in the other experiments, measurements of the pH of the highly buffered Locke's solution were made. For the longest periods in the constant temperature water bath, the pH descended from 7.2 to 7.0 at 42.0° C., the lowest value with the fragment method for any experiment being pH 6.9. Bacterial contamination was tested by subculture and occurred rarely (and only with the suspension method). Abscesses were very uncommon and in general the tumor inoculations were free of the stigmata of infection as a complicating factor. This is borne out by the histological study of the tumor inoculation sites.

The suspension of tumor material was tested at 42.0° C. since our experiments with other tumors have indicated that this temperature would give a shorter thermal death time than 41.5° C. Since the limit of viability at 42.0° C. centered around sixteen hours with the suspension method, it was not thought feasible to find the end point at 41.5° C. The first inoculations with single fragments were made in only one testis but in the last experiment, both testes were inoculated each with single fragments in the same animal since the tumor was so much damaged by these temperature ranges especially near the end point that metastases occurred rather infrequently. Furthermore, the number of takes was low so that in many cases tumor grew in only one testis or not at all.

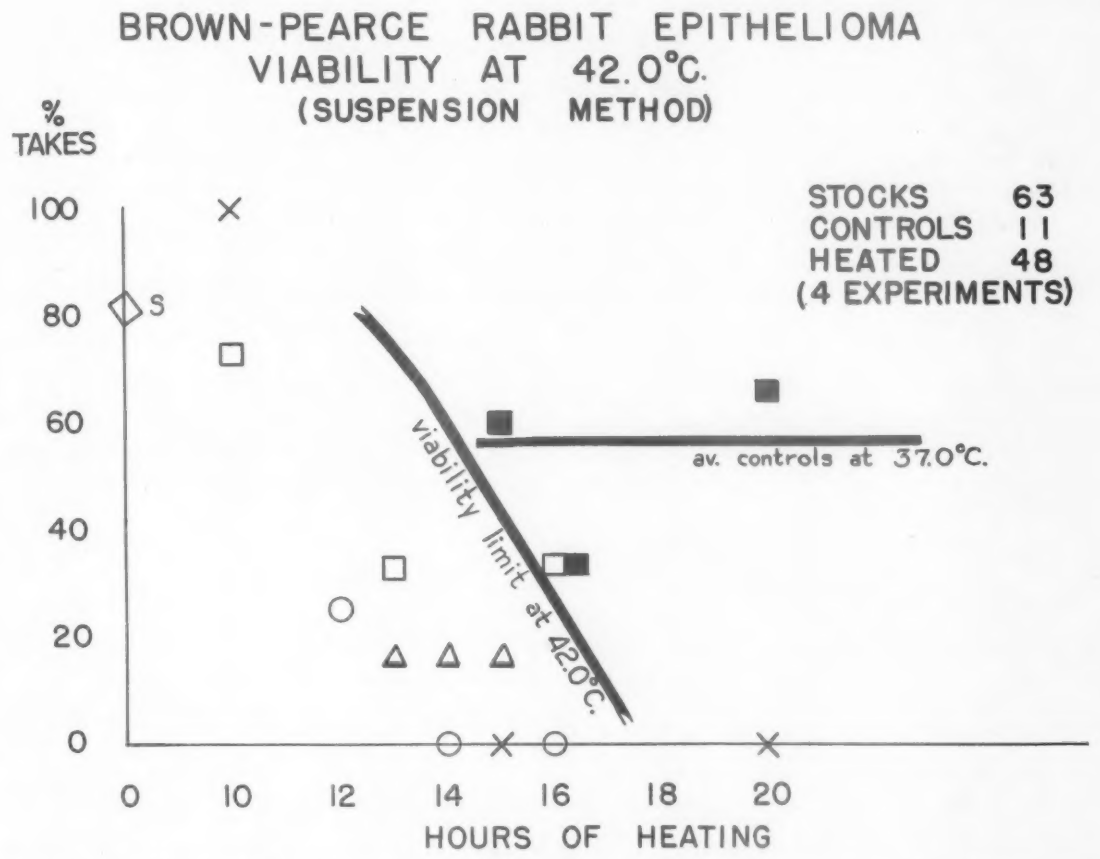


Chart IX. Incidence of takes at 42.0° C. using the suspension method of inoculation. The solid squares are the controls at 37.0° C. Each of the other four symbols represents an individual experiment. Each point is an average for 3 to 6 animals. The stocks (s) average 83 per cent takes.

## RESULTS

*Controls at 37.0° C.* Control tumor material employing both methods was maintained under similar conditions at 37.0° C. A few tests were made with the controls exposed to a temperature of 26.0° C. (to cover all the temperature gradients in the

TABLE IX

BROWN-PEARCE RABBIT EPITHELIOMA—THE INCIDENCE OF TAKES

Suspension Method

| | Stocks | | Hours of Heating | 37.0° C. | | | 42.0° C. | | |
|---|---|---|---|---|---|---|---|---|---|
| No. Inoc. | No. Takes | % Takes | | No. Inoc. | No. Takes | % Takes | No. Inoc. | No. Takes | % Takes |
| 63 | 52 | 83 | 10 | | | | 7 | 6 | 86 |
| | | | 11 | | | | | | |
| | | | 12 | | | | 4 | 1 | 25 |
| | | | 13 | | | | 9 | 2 | 22 |
| | | | 14 | | | | 10 | 1 | 10 |
| | | | 15 | 5 | 3 | 60 | 9 | 1 | 11 |
| | | | 16 | 3 | 1 | 33 | 6 | 1 | 17 |
| | | | 17 | | | | | | |
| | | | 18 | | | | | | |
| | | | 19 | | | | | | |
| | | | 20 | 3 | 2 | 67 | 3 | 0 | 0 |
| 63 | 52 | 83 | | 11 | 6 | 54.5 | 48 | | |

rabbit's testis), but no difference in the viability of the cells from that at 37° C. was observed. The percentage of takes with the *suspension* of the tumor was quite low, averaging approximately 56 per cent while the stocks averaged 83 per cent (Table IX). The spread of the latent period was considerable and difficult to assay.

TABLE X

BROWN-PEARCE RABBIT EPITHELIOMA—THE INCIDENCE OF TAKES

Fragment Method

| Stocks | | | Hours of Heating | 37.0° C. | | | 42.0° C. | | | 43.0° C. | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. Inoc. | No. Takes | % Takes | | No. Inoc. | No. Takes | % Takes | No. Inoc. | No. Takes | % Takes | No. Inoc. | No. Takes | % Takes |
| 384 | 376 | 98 | 5 | | | | | | | 4 | 4 | 100 |
| | | | 10 | | | | | | | 4 | 0 | 0 |
| | | | 13 | | | | 4 | 4 | 100 | | | |
| | | | 14 | | | | 4 | 3 | 75 | | | |
| | | | 15 | | | | 3 | 2 | 67 | | | |
| | | | 16 | | | | 3 | 2 | 67 | | | |
| | | | 17 | 6 | 5 | 83 | 4 | 4 | 100 | | | |
| | | | 18 | | | | 2 | 0 | 0 | | | |
| | | | 19 | | | | 2 | 2 | 100 | | | |
| | | | 20 | | | | 6 | 5 | 83 | | | |
| | | | 21 | | | | 8 | 3 | 38 | | | |
| | | | 22 | 7 | 5 | 72 | 8 | 2 | 24 | | | |
| | | | 25 | | | | 6 | 2 | 33 | | | |
| | | | 30 | | | | 6 | 0 | 0 | | | |
| | | | 35 | 6 | 5 | 82 | 6 | 0 | 0 | | | |
| 384 | 376 | 98 | | 19 | 15 | 79 | 62 | | | 8 | | |

With the *fragment method*, the percentage of takes averaged 79 per cent (Table IX) and the variation was relatively small. The 5 controls exposed for thirty-five hours averaged 84 per cent against a stock general average of 98 per cent, although the concurrent stocks took in all cases, i.e., 100 per cent. The *latent period averages* within the upper limits of the spread of the stocks. This is particularly true at the thirty-five hour period where 4 out of the 5 tumors had a latent period averaging 8.5 days (2 of eight days, and 2 of nine days).

*Effects at 42.0° C.* The time necessary to cause complete failure to take with the *suspension method* varied somewhat in

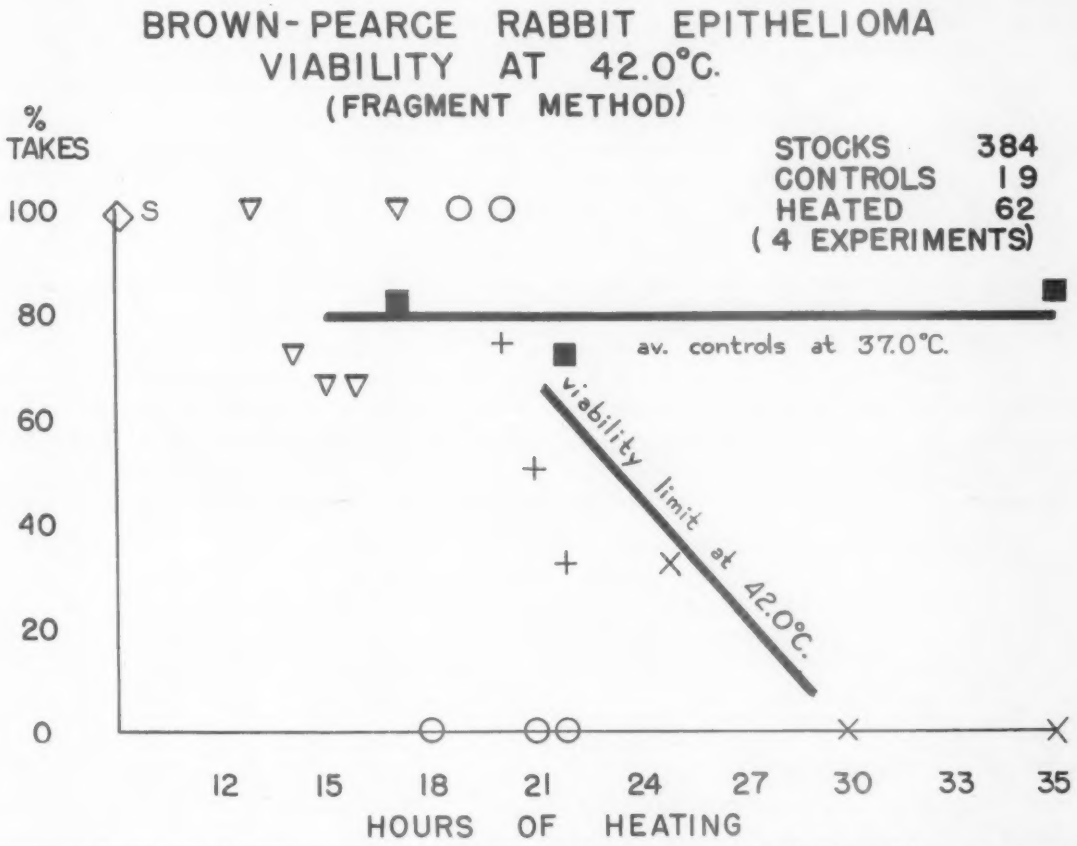


Chart x. Incidence of takes at 42.0° C. obtained with the fragment method. The solid squares represent the controls at 37.0° C. Each of the other four symbols represents an individual experiment. Each point is an average for 2 to 8 cases. The stocks (s) average 98 per cent in 384 cases, and 100 per cent in the 26 cases of the concurrent experiments.

(Chart XI and Table XI) increased to 11.6 days (19 cases), an increase over the stocks (5.6 days for 4 cases) which seems to be due to the experimental technique and the relative paucity of cases. It is probably fair to point out that there are no points for the periods up to thirteen hours, and that a large series in this region might reduce the average level more nearly to that of the stocks. Slightly over half of the controls, however, have a latent period (Chart XI) the different experiments, but in general covered the period between fourteen and twenty hours, the longest times being taken as the final point. Chart IX and Table VIII represent a summary of these experiments in percentage of takes for each individual experiment. The growth characteristics were difficult to analyze but in general show the same tendency as was found with the mouse and rat tumors.

With the *fragment method*, the spread of

the failure to take is between twenty-one and thirty hours, the latter being taken as the end point (Chart x and Table x). This is much longer than when the suspension method was used and probably, as pointed out in the method, is due to less mechanical damage to the tumor. The *latent period* (Chart xi and Table xi) increased as the thermal death time was approached, but there seemed to be little damaging effect except in the periods beyond sixteen hours of exposure. The average line drawn for 42.0° C. in Chart xi therefore does not pass through the control line at the ordinate, i.e., zero time of heating. The average line probably follows the control up to twelve and fifteen hours of exposure before deviating sharply upward as the damage from the temperature elevation becomes apparent. The *actively growing* period varied in general around the normal of the stock but the numbers in the longer periods are too small to be of much comparative value.

*Effects at 43.0° C.* Only one experiment testing five and ten hours (four fragments each) was undertaken at this temperature. All the fragments exposed for five hours grew but none survived the ten hour exposure (Chart xii). This illustrates the marked increased destructive effect of this temperature, i.e., there was a reduction of at least twenty hours in the limit of viability upon elevating the temperature 1° C. It should be emphasized that since this is only one experiment, the true end point for this tumor might well be some hours shorter if more groups of animals were tested in the thermal death time range. Thus it would appear without further test that the increase in temperature has an enhanced destructive effect as in the other tumors tested. The *latent period* (average twenty-one days) for the five hour heating was equivalent to that of the fragments heated beyond seventeen hours at 42.0° C. (Chart xi). The average

TABLE XI

BROWN-PEARCE RABBIT EPITHELIOMA

LATENT PERIOD (Days)

Fragment Method

| | Hrs. | 5 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 25 | 30 | 35 | Av. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Stocks | Days | | | | | | | | | | | | | | | | | | 5.6 |
| | Cases | | | | | | | | | | | | | | | | | | 24 |
| 37.0° C. | Days | | | | | | | | | 13 | | | | | 12 | | | 10.6 | 11.6 |
| | Cases | | | | | | | | | 4 | | | | | 5 | | | 5 | 14 |
| 42.0° C. | Days | | | | | 13 | 16 | 18 | 18 | 19 | | 24 | 23 | 35 | 20 | 18 | | | |
| | Cases | | | | | 4 | 3 | 2 | 2 | 4 | | 2 | 5 | 3 | 1 | 1 | | | 27 |
| 43.0° C. | Days | 21 | | | | | | | | | | | | | | | | | |
| | Cases | 4 | | | | | | | | | | | | | | | | | |

Suspension Method

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Stocks | Days | | | | | | | | | | | | | | | | | | 7.5 |
| | Cases | | | | | | | | | | | | | | | | | | 52 |
| 37.0° C. | Days | | | | | | | 9 | 11 | | | | 7 | | | | | | 8.7 |
| | Cases | | | | | | | 3 | 1 | | | | 2 | | | | | | 6 |
| 42.0° C. | Days | | 23 | | 41 | 18 | 5 | 9 | 12 | | | | | | | | | | |
| | Cases | | 5 | | 1 | 2 | 1 | 1 | 1 | | | | | | | | | | 11 |

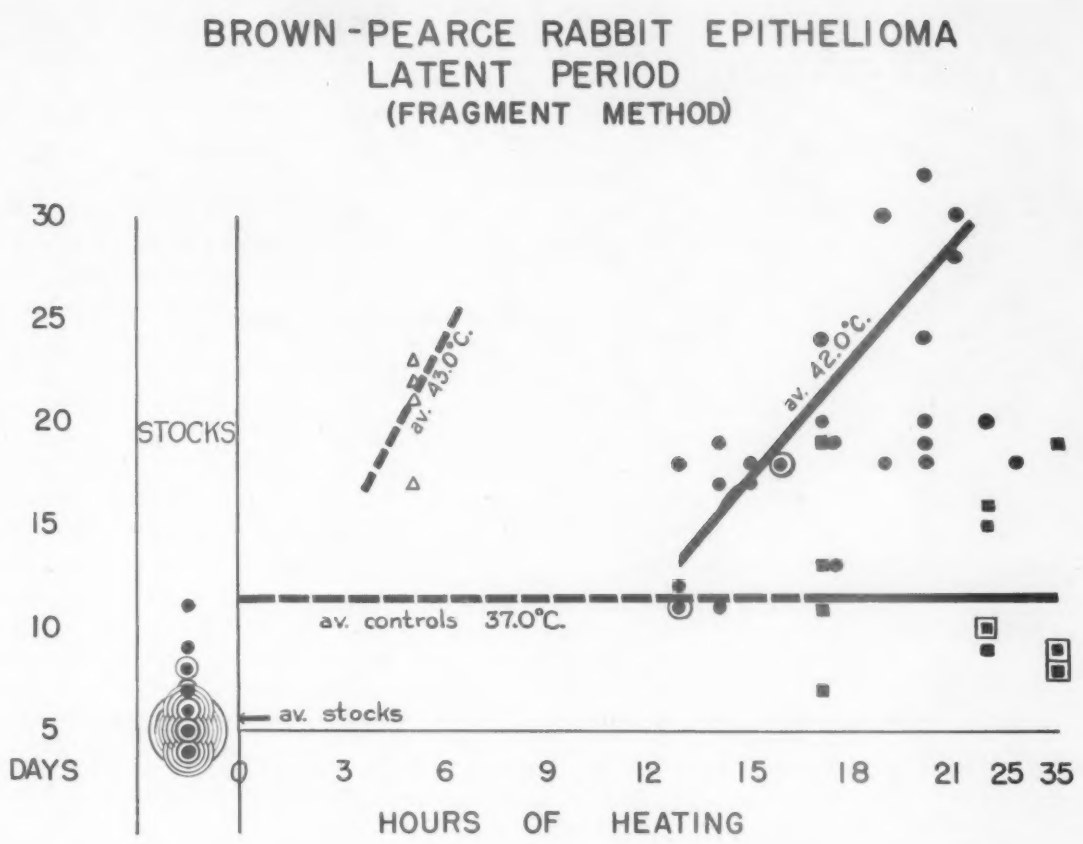


Chart xi. The latent period using the fragment method shows a stock average of 5.6 days while the controls average 11.6 days (squares). The heavy line is drawn through the averages for 42.0° C. The broken line for 43.0° C. is empirically drawn through the average for the one experiment. Each point represents an individual case.

line, although based on the average of a single experiment, probably should have a steeper slope than 42.0° C., judging from the findings with the other tumors.

As a probable further indication of injury to the tumor cells as a result of the exposure to the fever temperatures, it was observed that 12 out of 27 rabbits, or 44.5 per cent, showed no *local* extension or *metastasis* of the tumor from its original inoculation site after the implantation of tumor fragments heated at 42.0° C. In contrast, 7 out of 26 stocks, or only 26.9 per cent, showed no tumor spread from the inoculation site. Intermediate between these two above groups were the control tumor fragments heated at 37.0° C. which showed no extension in 4 out of 11 cases, or 36.4 per cent. Since the normal temperature of the rabbit's testis is considerably below 37.0° C., and since the temperature of the stock tumor fragments was not raised above that normal range, it might be expected that this comparatively slight degree of temperature elevation could have the effect of raising this non-spread percentage from the 26.9 per cent of the stocks to 36.4 per cent. However, the factor of mechanical damage resulting from the long period of shaking and the necessary extra handling of the fragments heated at either 37.0° C. or higher might also affect these results; on the other hand, a group of rabbits inoculated with fragments heated at 37.0° C. for thirty hours showed no significant difference in either the incidence of takes or tumor spread from another control group receiving fragment shaken for sixteen

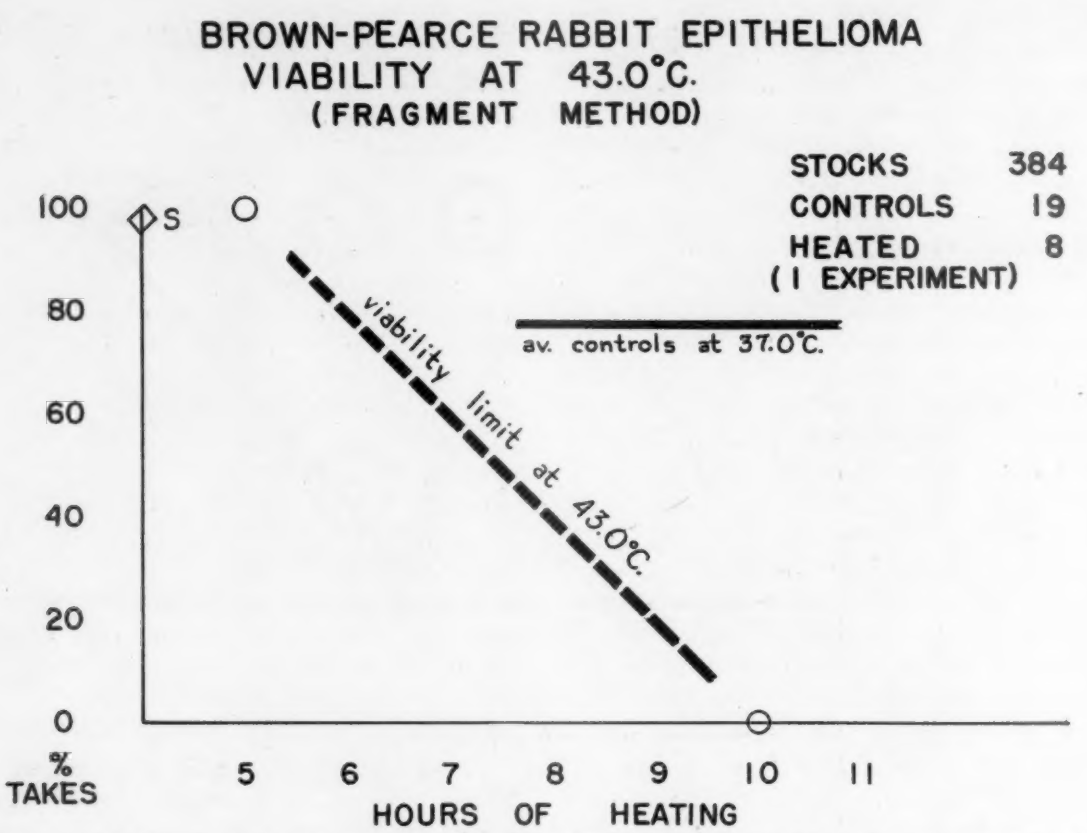


CHART XII. Incidence of takes of one experiment at 43.0° C. using the fragment method of inoculation. The same tumor material was employed here as indicated by the same symbols in Chart II. This is the only case where similar symbols indicate the same experiment in this paper.

hours at 37.0° C. Furthermore, there is the apparently significant difference between the percentage of tumor spread in the 37.0 and 42.0° C. groups, both of which received the same amount of shaking and handling and treatment except for the temperature difference. Thus, it is possible that the 42.0° C. temperature exposure in itself decreased the incidence of tumor spread.

## DISCUSSION

It should be emphasized that the ability of cells to resume growth after a given type and degree of injury depends in part upon the methods, conditions, and criteria employed to test their recoverability. Schrek[8] studied the lethal effects of 43.0° C. upon a suspension of tumor cells (rat carcinoma 256) using the staining of cells by eosin as an indicator of death of the cells. This temperature apparently resulted in a rapid reduction in the viable cells in four hours with none viable after eight hours of exposure. This would indicate a greater resistance to increased temperature than we have found, but the technique is quite different, and the ability of the cells to grow was not investigated. Also Wood and Prime[12,13] and Krontovski and Lebensen[5] have shown that tumor cells which would not take when inoculated in the normal, living animal would nevertheless apparently grow in tissue culture. However, it appears likely from the evidence gained here from the several criteria of histological study, ability to take, and the various tumor growth characteristics used in these studies, that irreparable damage was suffered by the majority of the cells receiving a sufficient exposure at these comparatively low temperatures (41.5 and 42.0° C.). That an increase of one-half degree (from 41.5

to 42.0° C.) should decrease the thermal death time approximately one-half is in keeping with the enhanced destructive effects of this temperature range for certain bacteria, i.e., gonococci (Carpenter, *et al.*[2] 1933). The *in vitro* destructive effect upon mouse sarcoma 180 and rat carcinoma 256 of a temperature elevation of such a relatively small amount above the normal for mouse and rat tissues seems to be of fundamental significance in the study of the biology of tumor cells. Time and intensity factors are as important here as in other biochemical and biological phenomena.

The thermal death time of seven and thirteen hours for rat tumor 256, and eight and fifteen hours for mouse tumor 180 at 42.0 and 41.5° C., respectively, compare very closely with each other under these experimental conditions. One might assume that two tumors of different characteristic cell types and origin might vary markedly from each other in their resistance to elevated temperature in such an *in vitro* test. It is not surprising to find more spread in the lethal times of the experiments done at 41.5° C., because this temperature is less effective than 42.0° C. in damaging the cells. The consistently sharp drop in the percentage of takes near the end point in each individual experiment, i.e., for different tumor generations, seems to indicate that this *in vitro* lethal effect is a fairly definite biological effect from the temperature elevation alone.

The latent period characteristics at both temperatures within each species (mouse and rat and rabbit) and also among the three species show very similar trends. Such growth characteristics are only perhaps of secondary importance, although they give additional information concerning sublethal but definite injury to the tumor tissue.

In general, these experiments show that the same type of results is obtained with the mouse, rabbit, and rat tumors tested, with the exception that the thermal death time of the rabbit epithelioma is considerably longer. This rabbit tumor is a more malignant and actively growing one. In the main, one might expect this variation in resistance to elevated temperature due to inherent characteristics of different species, one of which might be the normal temperature level of the host. The rectal temperature of the rabbit is subject to wide swings often considerably greater than is the case in the mouse and rat. Under normal housing and laboratory conditions it may fluctuate from 37.0 to 39.5° C. During excitement or fighting, it may rise to 41.5° C. Normal tumor temperatures in the testis at ordinary room temperature may range from 29.0 to 39.0° C. in the central portion with the temperature usually decreasing progressively as the periphery is approached. The relation of temperature gradients to tumor growth and *in vivo* temperature elevation will be discussed in another paper of this series.

## SUMMARY

1. An improved technique is described for the measurement of the *in vitro* thermal death time or survival times of mouse sarcoma 180, rat carcinoma 256, Jensen rat sarcoma, and the Brown-Pearce rabbit epithelioma at human fever temperatures.

2. The approximate *thermal death time* (failure of all tumor fragments to take) *in vitro* for mouse sarcoma 180 under these experimental conditions was found to be fifteen hours at 41.5° C. and eight hours at 42.0° C., and for the rat carcinoma, thirteen and seven hours respectively. With the *suspension method* the thermal death time for the Jensen sarcoma was ten hours at 41.5° C. and four hours at 42.0° C. For the Brown-Pearce rabbit epithelioma with the *suspension method* it is approximately twenty hours at 42.0° C., and with the fragment method approximately thirty hours at 42.0° C., and it is approximately ten hours at 43.0° C. using the *fragment method.*

3. Evidence of damage to the tumor cells by sublethal exposure to these temperatures is shown both in histological section and by the prolongation of the appearance time of the tumor after such irradiation.

4. A study of the actively growing period of the tumor (from a palpable tumor to exitus of the host from cachexia) indicates that these temperatures cause no permanent change in the growth characteristics for, if the tumor starts growing, in general it develops in the usual manner comparable to that of the stocks and controls. In the Brown-Pearce rabbit epithelioma there seems to be a slight inhibition of the ability of the tumor to spread (metastasize) after exposure to these fever temperatures.

## CONCLUSIONS

Temperatures of 41.5 and 42.0° C. are capable of damaging or destroying mouse sarcoma 180, rat carcinoma 256, Jensen rat sarcoma, and the Brown-Pearce rabbit epithelioma *in vitro* after appropriate periods of exposure.

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# EFFECT OF ROENTGEN RAYS ON THE TOXICITY OF BLOOD*

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## INTRODUCTION

ROENTGEN sickness is no infrequent occurrence at the present time because of the increased scope of roentgen therapy for malignant tumors and other pathological conditions. My investigation was prompted in the first place by a profoundly toxic reaction in a pet English setter, irradiated for the purpose of sterilization. It so happened that sterilization was not accomplished but the animal became extremely sick and came so near dying that I wondered whether the clinical picture of great depression and apparent toxemia was not due to some toxic substance generated by irradiation, and an attempt was made to demonstrate the presence of such a toxin in the animal's blood.

Ordinary pharmacological methods in which animals or animal tissues are used to detect various toxins in the blood of patients suffering from well-known diseases are not suitable for such an investigation. However, the writer and his collaborators have shown that by special *phyto*pharmacological methods, i.e., by the use of living plant-physiological test objects such as seedlings grown in nutrient solutions, the presence of even small amounts of certain toxins can be demonstrated in the blood of various animals, including the human being, which could not be detected by *zoö*pharmacological methods.[1,2,3,4,5,6,7] The technique employed in such work has been described by me in numerous papers and need not be detailed here.[8,9] Briefly, it consists of studying the growth or increment in length of the roots of *Lupinus albus* seedlings in standard physiological solutions as compared with other seedlings from the same batch of plants in similar solutions in which 1 per cent of whole blood or blood serum had been dissolved. Such seeds or seedlings are allowed to grow for twenty-four hours under standard conditions of temperature, light, etc., and the increment in root growth in pathological solution divided by increment of root growth of control seedlings is designated as the *phytotoxic index*.

## MATERIAL INVESTIGATED

In connection with studies of the effects of roentgen rays, blood specimens from ten kinds of animals were studied, and the present report is a summary of the results obtained in experiments on 30 rats, 25 rabbits, 5 cats, 2 dogs, 4 guinea pigs, 10 mice, 3 pigeons, 2 fish and a number of frogs. The procedure employed was as follows: Samples of normal blood were collected from the different animals *before* their irradiation and a second series was drawn *after* their exposure to varying doses of roentgen rays. Phytopharmacological examination was made of the blood serum of the large animals and of the whole blood of the small animals such as mice, rats and frogs.

The physical apparatus employed in this investigation was secured through the courtesy and collaboration of Dr. C. F. Burnam of the Howard A. Kelly Hospital, Baltimore, where all the animals were irradiated, and consisted of a constant potential electric transformer with water-cooled therapy tubes. The kilovoltage was 264; milliamperes, 30. The roentgen rays were filtered through a copper plate and an aluminum plate, each 1 millimeter thick. The animals were irradiated at a distance of 50 centimeters, the dosage for one minute being 105 r. The dosage of roentgen rays employed in various experiments

* Read at the New York Meeting of the Optical Society of America, February 25, 1938.

ranged from 200 to 1,000 r. In most of the experiments a single irradiation was employed but, in a small series of tests, the effect of repeated small doses or exposures to roentgen rays was also investigated.

## RESULTS

The subjoined tables set forth clear-cut and striking results and indicate the kind of animal used for the test, the roentgen-ray dosage employed and the phytotoxic indices of the respective specimens of their blood obtained before and after irradiation.

TABLE I

EFFECT OF ROENTGEN RAYS ON THE TOXICITY OF BLOOD

| Animal | Dosage | Normal Phytotoxic Index | Phytotoxic Index after Irradiation |
|---|---|---|---|
| Mouse | 250 r | Whole blood, 74% | After 24 hours, 52% |
| Rat | 300 r | Whole blood, 77% | After 24 hours, 52% |
| Guinea pig | 250 r | Blood serum, 76% | After 24 hours, 56% |
| Kitten | 250 r | Blood serum, 71% | After 24 hours, 54% |
| Rabbit | 300 r | Blood serum, 70% | After one hour, 68% |
| Rabbit | 300 r | Blood serum, 70% | After 24 hours, 55% |
| Rabbit | 300 r | Blood serum, 70% | After 72 hours, 48% |
| Rabbit | 300 r | Blood serum, 70% | After one week, 75% |
| Pigeon | 250 r | Whole blood, 63% | After 24 hours, 47% |
| Dog | 300 r | Blood serum, 75% | After 24 hours, 66% |
| Fish (pike) | 500 r | Blood serum, 75% | After 24 hours, 64% |
| Frog | 500 r | Whole blood, 55% | After 2½ hours, 27% |
| Frog | 500 r | Whole blood, 55% | After 24 hours, 23% |
| Mrs. Y. (carcinoma of breast) | 300 r | Blood serum, 68% | After 24 hours, 32% |

By means of numerous previous experiments the author and his coworkers have shown that the phytotoxic index of normal blood is from 70 to 75 per cent. A 1 per cent solution of whole blood has a phytotoxic index of 60 to 65 per cent. As Table 1 indicates, blood drawn from the various animals after their exposure to roentgen rays showed a definitely increased toxicity for *Lupinus albus* seedlings. The degree of toxicity varied widely, however, not only with regard to the animal studied but also with regard to the roentgen-ray dosage employed. Even more interesting was the finding that exposure to the roentgen rays did not *immediately* produce a toxic reaction of the blood. Although some toxicity could be detected in blood drawn a few hours after exposure to the rays, the greatest degree was usually found in samples drawn twenty-four hours after irradiation. This finding suggests that a toxic substance is gradually formed in the blood and liberated as a result of irradiation of various tissues of the animal body. This toxic reaction of blood to roentgen rays generally persisted for two or three days, after which the blood was gradually restored to its normal state. When the dosage of roentgen rays was very high, however, the toxic reactions continued for as long as a week, and the animals died after excessive irradiation. All the results reported in the present paper deal with experiments on animals. Only one human patient was studied in this connection. As soon as opportunity presents itself, I plan to follow the present research with a series of studies on clinical cases. Such an investigation will necessitate a close cooperation with radiologists.

## IRRADIATION OF VARIOUS AREAS

In order to ascertain the effect of roentgen rays on various tissues of the animal body, I performed a series of experiments on rats, in which different regions of the body were respectively exposed to equivalent doses of roentgen rays. Three areas of the body were thus irradiated. In the first

series, the rats' heads were exposed to roentgen rays; in the second, the thoracic portion; and in the third series, the abdominal region was irradiated. Samples of blood obtained from the rats thus irradiated were tested by phytopharmacological methods, and the phytotoxic indices obtained were compared. As Table II shows, it was found that the most toxic samples were drawn from rats of which the head had been exposed to roentgen rays. Next in toxicity were samples obtained from rats, especially the female, in which the abdominal region had been similarly treated; and blood samples obtained after irradiation of the thoracic region showed least toxicity. These findings were not surprising because from the physiological point of view brain tissue and certain abdominal glands, particularly the liver and ovaries, are susceptible to the effects of roentgen rays.

TABLE II

EFFECT OF ROENTGEN IRRADIATION OF VARIOUS PARTS OF RATS ON TOXICITY OF BLOOD (5 EXPERIMENTS)

| | |
|---|---|
| Controls | Phytotoxic index, 70% |
| Whole cat irradiated with 250 r | Phytotoxic index, 60% |
| Head irradiated with 250 r | Phytotoxic index, 48% |
| Chest irradiated with 250 r | Phytotoxic index, 61% |
| Male abdomen irradiated with 250 r | Phytotoxic index, 60% |
| Female abdomen irradiated with 250 r | Phytotoxic index, 50% |

Continuing the investigation of the effect of roentgen rays on the brain, I carried out experiments on rats which were irradiated all over the body and later killed for biochemical examination of fresh brain and muscle tissues. Such tissue was studied in respect to its oxydase content by means of the well-known Thunberg method described in detail elsewhere by myself and collaborators.[10] Tables III and IV illustrate some of the results obtained. It will be noted that the rapidity of oxidation, indicated by the time required to decolorize the standard methylene blue solution, was lengthened both for muscle tissue and brain tissue. It was surprising to note that the oxydases of the muscle were more affected than those of the brain. This was true both in experiments in which the tissues were removed within twenty-four hours after exposure to the roentgen rays, as shown in Table III, and also in cases where the animals were irradiated three days before extirpation of the muscle and brain tissues.

TABLE III

EFFECT OF ROENTGEN RAYS ON MUSCLE AND BRAIN OXYDASES OF RATS

| Number of Experiments | Substance Tested | Decolorization Time |
|---|---|---|
| 5 | Normal muscle | 44 minutes |
| 5 | Muscle irradiated with 250 r | 52 minutes |
| 3 | Normal brain | 25 minutes |
| 3 | Brain irradiated with 250 r | 30 minutes |

TABLE IV

EXPERIMENTS WITH OXYDASES FROM RATS THREE DAYS AFTER IRRADIATION WITH 600 r

| Preparation | Decolorization Time |
|---|---|
| Normal muscle | 60 minutes |
| Irradiated muscle | 74 minutes |
| Normal brain | 24 minutes |
| Irradiated brain | 28 minutes |

## DISCUSSION

The results of these experiments definitely establish the fact that the blood of different animals, exposed to varying doses of roentgen rays, acquires certain toxic properties which can be demonstrated by the use of plant-physiological test objects. The degree of toxicity thus demonstrated is dependent on the species of animal and more particularly on the quantity of roentgen rays administered. Moreover, the toxic reaction of the blood does not immediately follow exposure to roentgen rays and is usually not fully developed until twenty-four hours later. Such a finding, of course, suggests a toxic basis for so-called roentgen sickness and raises the question as to whether there is any pharmacological means of preventing or minimizing the formation of such toxic bodies in the blood. With this

idea in mind I have been examining the effect of a number of substances recommended as preventives of roentgen sickness. Among these are Congo red and various vitamins, particularly vitamin $B_1$, which, in a recent publication, Martin and Moursund[11] claim to have found of value in preventing irradiation complications. Pharmacological experiments were carried out on the blood of animals, especially of rats, which were treated with Congo red and vitamin $B_1$, respectively. The phytotoxic index of animals to which Congo red was administered remained unchanged. Blood from such rats still gave a low phytotoxic reading, indicating great toxicity. It was demonstrated that vitamin $B_1$, however, did tend to reduce the toxicity of the animals' blood, and even more striking detoxification was effected by extracts of *Melanoplus differentialis*, a species of grasshopper which I have found contains certain vitamins, including $B_1$.

SUMMARY

1. Phytopharmacological tests of blood drawn from various animals before and after exposure to roentgen rays revealed an increased toxicity after such irradiation.

2. The toxic substance formed and liberated in the blood by such irradiation is not fully developed until twenty-four hours after exposure to roentgen rays.

3. Blood from a series of rats, with different parts of the body exposed to aliquot doses of roentgen rays, showed varying toxicity, the most toxic specimens having been drawn after irradiation of the brain and the next most toxic after irradiation of the female abdomen.

4. An investigation of chemical compounds which may exert an antidotal action by decreasing formation of such toxic bodies in the blood is in progress.

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# THE SIGNIFICANCE OF ASYMMETRY OF THE PORI ACUSTICI AS AN AID IN DIAGNOSIS OF EIGHTH NERVE TUMORS

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TUMORS of the acoustic nerve are of particular interest because they constitute from 8 to 10 per cent of all brain tumors. They are benign and, if diagnosed early, are amenable to surgical intervention.

Since the time of Cruveilhier and Weiglein, the majority of reports concerning necropsies and operations mention a projection of the tumor into the porus acusticus, which is described as being more or less dilated. This observation led Henschen to attempt to demonstrate enlargement of the porus acusticus by means of roentgenograms. In 1912, he reported a series of cases in which roentgenograms of the skull had been made.

Cushing, in his monograph on acoustic tumors, reports a number of cases in which roentgenograms were made. In 4 of his cases, definite enlargement of the porus acusticus was shown; in 6 cases questionable enlargement, demonstrable more as lack of distinct outline than as widening of the canal, was found. A careful review of his own, Josefson's, and Henschen's published cases led him to the conclusion that frequently the external and not the internal auditory canal had been described. He considered the results generally unsatisfactory, especially in early cases where successful demonstration of an enlarged porus acusticus would be of great help. However, he expressed the belief that increased knowledge would eventually lead to detection of early cases roentgenologically, before the appearance of typical angle signs and symptoms. This would be a real step in advance.

These unsatisfactory results, we now know, were partially due to inefficient mechanical equipment but more largely attributable to the position of the patient's head in which the exposures were made. For these studies the so-called Schüller technique for demonstration of the mastoid had been used. This technique superimposes the shadow of the internal auditory meatus on that of the external auditory meatus, the principal ray traversing the length of each canal. By use of this position it is evident that, if any considerable portion of the porus acusticus remained intact, the intact portion would cast a normal shadow and the dilated portion would be rendered indistinct by the surrounding and overlying bony structures.

Since that time apparatus and technique have improved until now there are a number of standard methods for obtaining satisfactory views of the pyramids and the porus acusticus. The successful use of these technical advances is proved by numerous cases reported in the literature of the past decade in which dilatation or destruction of one or both internal auditory canals was well shown.

We have used the various positions recommended for demonstrating the petrous pyramids and have come to the conclusion that an anteroposterior position, with the head placed at such an angle that the shadow of the pyramids is cast through the orbits, is most conducive to demonstration of the internal auditory meatus. We base this preference on considerable experience with the other more widely used projec-

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tions and on the anatomic fact that, although the petrosae lie in the base of the skull at an angle of approximately 45 degrees to the sagittal plane, the pori enter the pyramids at such an angle that the long axes form a right angle with the sagittal plane and thus are parallel with the film when the recommended position is utilized.

The basal projections reveal many confusing shadows, especially that of the carotid canal over the porus acusticus. The Towne position is excellent for disclosing erosion of the posterosuperior surface of the pyramid but, in this position, confusing shadows may be cast over the porus acusticus. The positions of Stenvers and of Hodgson are excellent for the pyramid as a whole, but produce a foreshortened though not unsatisfactory image of the porus acusticus. However, in these positions, the pyramids are not projected on the same film for comparison.

Roentgenology, in the past fifteen years, has achieved a definite and important place in the diagnosis of these tumors. However, the majority of cases, in which positive roentgenograms are obtained, have advanced to a stage at which the diagnosis is unusually clear by other methods.

The petrosae of the temporal bone have been called the most variable bones in the body and the truth of this statement is evident to anyone who has observed a number of roentgenograms of this region. Because of the variation noted between the pyramids and pori acustici of the two sides, we studied, through the cooperation of the Section on Pathologic Anatomy, a number of bones removed at necropsy in the hope of establishing the normal limits of size and appearance of the porus acusticus more definitely than is now the case. Such information should facilitate an earlier roentgenologic diagnosis of abnormal cases.

Because of the extreme hardness of the bones and the marked differences in caliber of the porus acusticus in various portions and because it was not desirable to destroy more bones than necessary, it seemed best to carry out most of the measurements by means of roentgenograms. For this purpose, a mixture of white lead and barium sulfate was prepared and worked to the consistency of putty. A number of canals were filled with this substance and exposures made in two positions. The "putty" was then removed and the bones exposed again in the same two positions. As we had hoped, the contrast between the bone and the air containing porus acusticus was sufficiently great to make measurements equally satisfactory by either method. For this reason and because the putty obscured bone detail, in which we were interested, we discontinued use of opaque media for this work.

Roentgenograms of the bones were made in pairs, using two positions: the first, with the bones horizontal and in close contact with the film, the second, with the bones arranged at an angle of 45 degrees with the film so that the long axis of the porus acusticus was parallel with the film. Because a 7-foot target-film distance was used, and because the porus acusticus, at most, was no more than 1½ inches from the film, the magnification of the shadow obtained was negligible.

For the purpose of measurement, the films were placed in a lantern so arranged that the image was magnified exactly ten times. By excluding all outside light very good detail was obtained. The measurements are, we feel, accurate within 0.2 mm., disregarding the minimal distortion inherent in roentgenograms made in this manner.

In all, 509 individual bones were examined; of this number, 250 pairs were used for comparative studies. These bones, as has been stated previously, were normal specimens obtained at necropsy and in no instance was there any evidence of erosion or other abnormality.

The roentgenograms were measured carefully and the greatest diameter and configuration of the porus acusticus noted. For the purpose of simplicity the configuration or shape of the canal was divided into four groups: straight, narrowed medially,

narrowed laterally, and oval. The porus acusticus was considered straight when the diameter as seen in the roentgenogram varied not more than 0.5 mm. If the portion nearest the internal ear exceeded the diameter of the open end by more than 0.5 mm., the porus acusticus was considered to be narrowed medially. If the reverse was true, it was considered to be narrowed laterally. If the midportion of the canal was greater in diameter than either end it was considered oval in shape.

The variation in diameter between the two ends of the canal was frequently 1 or 2 mm., and, in some cases, as much as 3 or 4 mm. The variation in diameter of the pori acustici studied was remarkable. The maximal diameter noted was 11 mm., the minimal 2.5 mm. The average of the entire group was 5.23 mm. The average for each side was 5.24 mm. for the right and 5.22 mm. for the left. The diameters measured did not fall predominantly into any one group; 54 pori acustici measured between 6.0 and 6.5 mm. in diameter and 42 measured between 3.5 and 4.0 mm. The largest single group, 92 in number, ranged from 4.5 to 5.0 mm. in diameter (Table 1).

In 250 cases the porus acusticus of the right side was compared with that on the left in the same skull. Here, again, there was considerable variation. If the variation was no greater than 0.5 mm., the pori acustici were considered alike. If the variation was greater than 0.5 mm., they were considered dissimilar. One hundred and three pairs were similar, the remaining 147 pairs dissimilar. The diameter of the two sides varied between 0.5 mm. and 1.0 mm. in 84 pairs, between 1.0 and 1.5 mm. in 41 pairs, between 1.5 and 2.0 mm. in 17 pairs, between 2.0 and 2.5 mm. in 3 pairs, and 2.5 mm. in 2 pairs. As might be expected, neither side was predominantly larger (Table 1).

An equally marked variation was found in the shape or configuration of the pori acustici. The shape was considered straight in 305 bones, oval in 61 bones, narrowed medially in 81 bones, and narrowed laterally in 62 bones. The right and left sides of the same skulls were compared and were found to be alike in 174 cases and dissimilar in 76 cases. In cases in which the shape of the pori acustici was unlike, no single combination of shapes such as straight and oval, or straight and narrowed medially was predominant.

Examination of specimens obtained at necropsy gave evidence that the thin posterior wall of the internal meatus usually is destroyed to some extent by the tumor mass which causes dilatation of the porus, with consequent shortening of the canal. Since the mesial and lateral borders of the posterior wall are frequently clearly shown in roentgenograms of the skull, it seemed worth while to measure the depth of the porus acusticus directly in a number of cases. The depth from the superior part of the area cribrosa to the most mesial point on the concave margin of the posterior wall of the canal was measured in 100 cases (200 bones) and the measurements were compared. The average depth was found to be 7.9 mm. on the right side and 7.8 mm. on the left side. The deepest porus acusticus was 16 mm. in depth and the shallowest 3 mm. in depth. The majority measured between 4 and 10 cm. in depth (Table 1).

Considerably more uniformity was found on comparison of the two sides of the same skull although the variation was marked. One hundred matched pairs were compared with each other, 27 pairs varied in depth less than 1 mm. and were considered alike, 38 pairs varied between 1 and 2 mm., 23 pairs between 2 and 3 mm., and 7 pairs between 3 and 4 mm. The greatest variation was 5 mm. noted between 1 pair of bones (Table 1).

The diameter of the open or mesial end of the porus acusticus was measured directly in 100 cases. The average diameter was found to be 6.2 mm. for the right pori acustici and 6.1 mm. for the left pori acustici. The variation in size was in every way comparable to the variations noted in the roentgenogram, as was the variation

TABLE I

DATA OBTAINED FROM STUDY OF PORI ACUSTICI

Study of 509 bones

| Diameter of pori acustici, mm. | 2 | 2.5 | 3 | 3.5 | 4 | 4.5 | 5 | 5.5 | 6 | 6.5 | 7 | 7.5 | 8 | 8.5 | 9 | 10 | 11 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of specimens | 3 | 16 | 10 | 42 | 74 | 92 | 80 | 65 | 54 | 29 | 19 | 12 | 8 | 3 | 1 | 1 | |

Variation in diameters of right and left pori acustici of same skull in 250 cases, measured by roentgenologic examination

| | Cases in which right porus was larger than left porus of same skull | | | | | | | Cases in which left porus was larger than right porus in same skull | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Difference in diameter, mm. | 0.0 | 0.5 | 1.0 | 1.5 | 2.0 | 2.5 | 3.0 | 0.0 | 0.5 | 1.0 | 1.5 | 2.0 | 2.5 | 3.0 |
| Number of cases | 52 | 45 | 20 | 10 | 1 | 1 | | 53 | 39 | 21 | 7 | 2 | 1 | |

Distribution of depth of 200 normal pori acustici
Distance from most concave part of posterior wall to deepest portion of area cribrosa

| Depth, mm. | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of specimens | 5 | 22 | 28 | 37 | 40 | 20 | 18 | 13 | 6 | 6 | 3 | 1 | 1 | |

Comparison of depth of right porus acusticus with left porus acusticus of same skull, 100 cases

| | Both sides within 1 mm. of same size | Depth of right porus greater | | | | | Depth of left porus greater | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Difference in size, mm. | | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 6 |
| Number of pairs | 27 | 21 | 12 | 4 | 2 | | 17 | 11 | 3 | 2 | 1 | |

Comparison of diameters of right porus acusticus with left porus acusticus of same skull, 100 cases

| | Both sides within 0.5 mm. of same size | Diameter of right porus larger | | | | | Diameter of left porus larger | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Difference in size, mm. | | 0.5 | 1.0 | 1.5 | 2.0 | 2.5 | 0.5 | 1.0 | 1.5 | 2.0 | 2.5 |
| Number of pairs | 29 | 18 | 9 | 4 | 3 | | 14 | 18 | 3 | 2 | |

between the pori acustici of the same skulls (Table 1).

In order to check the shape and size directly, 30 pairs of bones were cut through at right angles to the length of the porus acusticus at the middle point of the canal. These pori acustici were measured directly and compared. The average for each side was 5.2 mm. The variations in size corresponded well with the variations noted in the roentgenograms.

The shape of the porus acusticus in cross section may be divided roughly into two types, oval or heart-shaped, and round or square. The long oval type predominated. In the majority of instances, the long diameter of the porus acusticus was parallel with the coronal plane of the skull.

In many cases, however, the long diameter was perpendicular to the coronal plane. The plane of the long diameter frequently may vary between the two sides of the same skull. Because of this fact, the diameter of the porus acusticus as revealed in a roentgenogram made in any single position will not always represent the greatest diameter.

In summarizing, one is forced to conclude that variations in diameter from 2.5 to 11 mm. may be normal and that variations of as much as 2.5 mm. between the two sides, while unusual, also may be normal. Likewise, variations of 5 mm. in depth between the two sides of the same skull, where demonstrable, may be normal.

For the purpose of further checking these normal variations against abnormal cases, petrosae were obtained at necropsy in 10 cases of acoustic neuromata. These cases are not as satisfactory as could be hoped for, inasmuch as the history was of long duration in each instance and the diagnosis was evident without the aid of roentgenologic examination.

In a number of these cases measurements were made directly, in others as the tumor was still intact in the porus acusticus, the bone was examined roentgenologically and measurements taken from the roentgenogram.

## REPORT OF CASES

Case I. The symptoms were of three years' duration. The tumor was on the right side, the right pyramid was thinned to a great extent, and the porus acusticus was markedly dilated. The greatest diameter as revealed by roentgenograms was 11.5 mm. and the smallest diameter, at the closed end, was 7 mm. In shape, it was narrowed laterally. The left porus acusticus was straight in shape and measured 7.5 mm. in its greatest diameter; thus, there was a difference of 4 mm. between the two sides (1.5 mm. greater than the greatest normal variation noted). Likewise, as has been stressed in most published reports, there was a great difference in the density of the two apices. We were disappointed to note that the erosion was smooth and in no way distinguishable from the outline of a normal porus acusticus as far as fine detail was concerned. The depth of each side was 3 mm. and 6 mm. respectively. This difference of 3 mm. although greater than usual, was not abnormal.

Case II. This patient had typical symptoms and gave a history of one year's duration. The tumor was on the right side and the apex was greatly thinned. The outer one-fourth of the meatus of the affected side was dilated to a diameter of 13.5 mm. The middle fourth measured 7 mm. in diameter and the deepest fourth measured 5 mm. in diameter. The normal porus acusticus on the left side belonged to the narrow mesial class, the diameter at the outlet being 4 mm. and the diameter laterally increasing to 6 mm. There was a difference of 7.5 mm. in the greatest diameter between the two sides. The affected porus acusticus measured 4 mm. in depth, the normal porus acusticus 6 mm. This difference is not unusual.

Case III. This patient gave a history of two years' duration and the tumor was protruding from the left porus acusticus. The greatest diameter of the left porus acusticus was 9 mm., occurring in the mesial fourth. The mesial fourth measured 6 mm. in diameter and the lateral fourth measured 4 mm. The porus acusticus on the right side was straight and measured 5 mm. in greatest diameter.

Case IV. In this case the right porus acusticus was affected. There was a history of five years' duration and symptoms were typical. The canal appeared shortened, straight, and not clearly defined. The greatest diameter that could be measured was 6 mm. The apex was greatly thinned. The porus acusticus of the normal side measured 5 mm. in diameter and was straight. In this case, the most marked difference was in the thinning of the affected apex. Both pori acustici were well within normal limits. If this tumor was of peripheral origin, the growth and expansion occurred in a mesial direction. The difference of 1 mm. in depth of the two sides was certainly well within normal limits.

Case V. This patient gave a history of thirteen years' duration, and a large tumor was found projecting into the dilated left porus acusticus. The porus was narrowed laterally, measuring 5.5 mm. in diameter at the closed end and 7 mm. at the mesial end. A large air cell was present above the porus acusticus and there was no evidence of erosion of the tumor

into it. The left apex was markedly thinned. The normal right porus acusticus measured 4.5 mm. and was straight. The difference in size between the two sides was within normal limits.

Case VI. This patient gave a history of three years' duration and had typical symptoms. Both pori acustici appeared small and short, both were straight, and each measured 4 mm. in the greatest diameter. The right apex, however, was markedly eroded and thinned by the tumor.

Case VII. This patient gave a history of two years' duration. The left side was affected. The apex was markedly thinned and the porus acusticus greatly dilated, appearing somewhat oval in outline. Erosion had reduced the superior wall of the porus to paper-like thinness and, in the roentgenograms, the erosion appeared to extend entirely through the bone in one small region. The right porus acusticus and apex appeared normal; the porus was narrowed laterally and measured 5.5 mm. in the greatest diameter.

Case VIII. This patient gave a history of one year's duration. The shadow of the right porus acusticus in the roentgenogram was largely obliterated, the mesial portion of the dense bone about the cochlea and the entire pyramid mesial to this was greatly thinned. The demonstrable dilated open end of the porus acusticus measured 12 mm. in diameter on the specimen but could not be seen in the roentgenogram. The porus acusticus on the normal side was very large and the edges appeared blurred and hazy. It was oval in shape and measured 7 mm. in the greatest diameter.

Case IX. This patient gave a typical history of five years' duration. The left porus acusticus measured directly was 8×4 mm., the right 6×5.5 mm. When roentgenologic examination was made at the usual angle, both pori acustici appeared to be of the same size and were straight in shape. The apex of the affected side was slightly increased in density rather than rarefied as is usually the case.

Case X. This patient gave a history of four years' duration. The tumor was on the left side. Measured directly, the greatest diameter of the left porus acusticus was 9 mm. and that of the right porus acusticus was 7 mm. The left porus was 9 mm. deep and the right 7 mm. deep, a reversal of what might be expected. The roentgenograms made with the bones in the usual position were surprisingly similar. There was but 1 mm. difference in the size of the greatest diameter of each side and both pori acustici were narrowed laterally to a marked extent. The walls on the affected side were slightly indistinct and the apex somewhat thinned.

## SUMMARY

This study would appear to indicate that, in the majority of cases of acoustic tumor, the porus acusticus is dilated and the apex markedly thinned. It is interesting and important to note that the most marked bone changes occurred in those patients who gave the shortest histories. It is equally apparent that, although roentgenologic examination may offer valuable confirmatory evidence, in the light of this work it cannot be used to rule out the presence of tumor. Thinning of the petrous apex and dilatation of the porus acusticus, if marked, are diagnostic in themselves. Valuable supporting evidence, occasionally present, may be found in the shape of the porus acusticus (which should be narrowed laterally) and in erosion and elevation of the petrous ridge.

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# THE USE OF THE ROENTGEN RAY IN OBSTETRICS*

## PART III. THE MECHANISM OF LABOR

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DURING the last five years we have accumulated a series of approximately 2,000 roentgenologic examinations from which to study pelvic morphology and the mechanism of labor. In approximately 1,000 cases the roentgenologic examination was obtained *during labor*. In numerous instances the examination included two and three stereoroentgenograms at suitable intervals, it being thus possible to observe descent, flexion, moulding, and rotation of the head in relation to the pelvic type and the pelvic soft parts.

Flexion and moulding of the fetal head occur in varying degrees in all labors when it meets bony or soft-part resistance. From the standpoint of fetal-pelvic relationships, however, two other factors warrant consideration: namely, the changes which occur in the direction of the long axis of the head as it is forced and guided in a certain axis through the pelvis, and the position of this axis in relation either to the symphysis in front or to the sacrum behind. The principle of these two variable factors is illustrated in Figure 1. The long arrow curved posteriorly represents the course commonly followed by the fetal head during engagement and descent; while variations in the length of distance A or B will indicate whether this curved axis of descent is taking place in the *fore pelvis* (anterior segment), through the *midpelvis*, or through the *posterior pelvis* (posterior segment).

### I. THE ACT OF ENGAGEMENT THROUGH A CURVED AXIS OF DESCENT

At term, just before the onset of labor, the long axis of the fetal head may show the variable degrees of asynclitism or angulation to the inlet illustrated in Figure 2. The posterior parietal position is also known as Litzmann's or Varnier's obliquity (Fig. 2, *A*). The anterior parietal position frequently is referred to as Nägele's obliquity (Fig. 2, *B*). These extreme positions are rare in occurrence. In the majority of instances, engagement begins with the head assuming a moderate degree of asynclitism and showing a tendency toward a posterior parietal presentation (to a lesser degree than shown in Fig. 2, *A*). The act of engagement in normal labor is illustrated diagrammatically in Figure 3, *A*. The posterior parietal bone first overhangs the inlet with the sagittal suture directed downward and forward toward the symphysis.

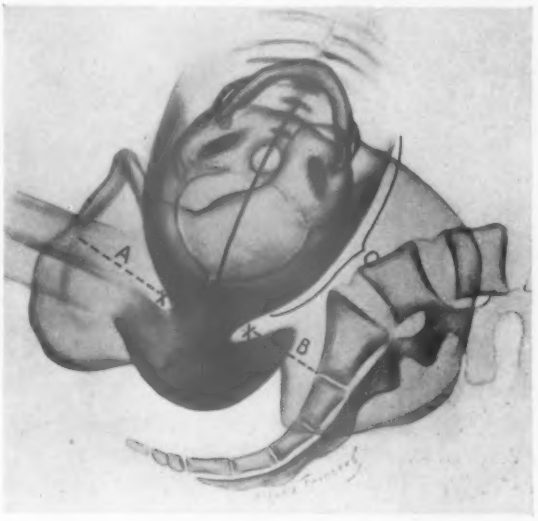


FIG. 1. Two important factors in the mechanism of labor diagrammatically illustrated. First, the mechanism of engagement and descent illustrated in Figure 3, *A*, takes place in a downward and backward direction along the axis of the long curved arrow. Second, through variations in the lengths of A or B this axis of descent may take place in the fore pelvis or through the posterior pelvis. (Courtesy of *Am. J. Obst. & Gynec.*)

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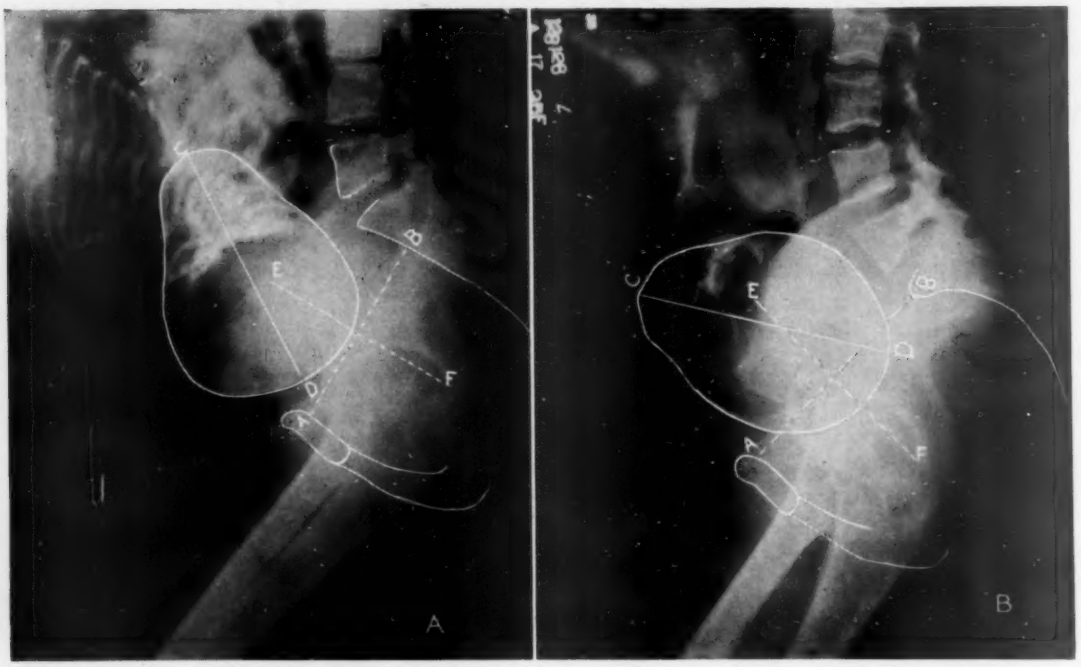


FIG. 2. *A*. Lateral roentgenogram early in labor. Extreme posterior parietal position at inlet. Such a marked degree is rare. AB—first plane at inlet and true conjugate diameter. CD—long axis of fetal head. EF—perpendicular to inlet through midpoint of true conjugate diameter. Note relationship of CD to EF and AB. (Courtesy of *Am. J. Obst. & Gynec.*)

*B*. Lateral roentgenogram early in labor. Extreme anterior parietal position so rare in this degree as to be considered an obstetrical curiosity. AB—first plane of inlet and true conjugate diameter. CD—long axis of fetal head. EF—perpendicular to inlet through midpoint of true conjugate diameter. Note relationship of CD to EF and AB.

The anterior parietal bone descends behind the symphysis in a downward and backward direction until the head is fitting squarely in the pelvic canal. As a rule, by the time the head has descended to fill the completely dilated cervix, its long axis may be found almost parallel with the sacrum. When the diagrammatic representation of this mechanism illustrated in Figure 3, *A* is applied to Figure 1 and the head is made to descend in the direction of the long curved arrow, the general character of the curved axis of this descent will become apparent. This mechanism has been described in obstetrical texts as the type which occurs in flat pelves. It is the reverse of the concept of synclitism illustrated in Figure 3, *B*, which is the mechanism commonly referred to in modern obstetrical discussions on this subject.

The lower uterine segment and cervix, while dilating in active labor, serve as a guiding factor and direct the head downward in this curved axis of descent. Scant reference has been made to the importance of this factor in recent obstetrical literature. Barnes[1] described the principle quite accurately by stating that the anterior aspects of the lower uterine segment acted as a "valve" or "inclined plane" directing the head downward and backward. Parvin[2] and others inferred the mechanism when they spoke of a "dynamic" axis of descent caused by soft parts which did not always correspond with the so-called "static" axis of the pelvis itself.

### 2. VARIATIONS IN THE POSITION OF THE CURVED AXIS OF DESCENT WITHIN THE PELVIS

The study of any series of labor films will show examples similar to the three varia-

tions illustrated in Figure 4. The orderly manner in which the head descends in each individual example has led us to suspect that the head does not descend by chance through any of these three possible axes, but rather that certain supporting structures of the lower uterine segment and cervix help to determine the position of the axis of descent in each case. The position of the lower uterine segment and cervix is dependent upon the fascial supports of the uterus, i.e., the uterosacral ligaments behind, the fascial bands attached posteriorly and laterally to the pelvic side wall, and those stretching anteriorly between the isthmic portion of the uterus and the symphysis under the bladder. The physical state of the fascial attachments and their reaction to the forces of labor may cause a change in the position of the cervix and direct the head forward into the fore pelvis or downward and backward into the posterior pelvis (Fig. 4, *A* and *C*).

In normal labor the stereoroentgenograms show that in the majority of cases the mechanism of engagement and descent just described occurs along an axis in the posterior pelvis. This observation supports the contention that the axis of the lower uterine segment and cervix is commonly maintained in this posterior region by its fascial supports. For this reason, the head is made to descend into the most ample part of the pelvic cavity—the posterior segment. The head, descending in the position determined by the shape of the inlet or the soft parts, descends to the bottom of the posterior pelvis. At this level, anterior rotation from the occipitoposterior or transverse positions begins and is completed when the head is forced downward and forward to a lower level in the outlet itself.

The efficiency of this normal mechanism is seen to advantage when an average-sized child is delivered easily through an abnormal pelvis. Perfect adjustment between head and pelvis is observed in the study of roentgenograms obtained during labor under such circumstances. No better example of this normal mechanism in an abnormal pelvis can be found than the one shown in Figure 5. That a posterior axis of descent

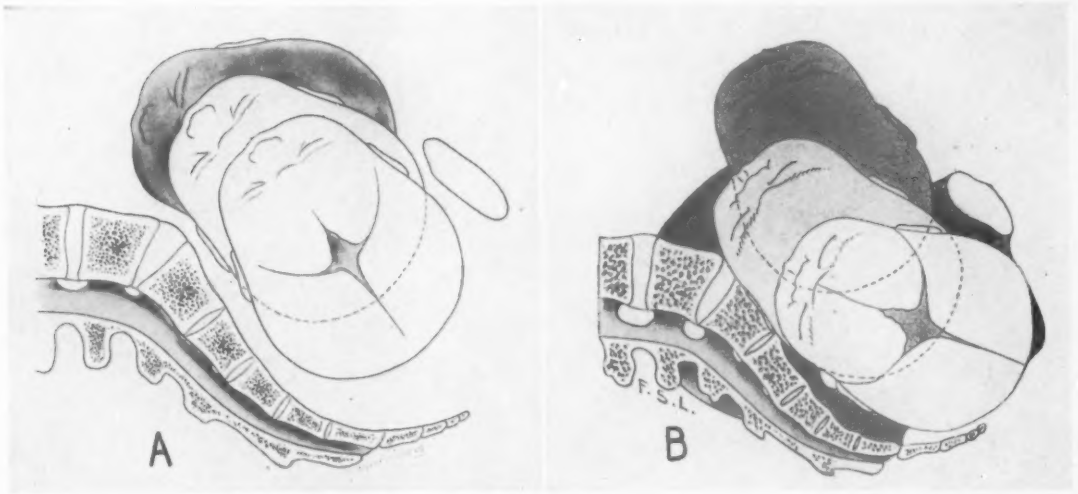


Fig. 3. *A*. The common mechanism of engagement and descent as revealed by this investigation. The head engages from a posterior parietal presentation with the sagittal suture of the head pointing toward the symphysis. The anterior parietal bone descends behind the symphysis in a downward and backward direction. (Courtesy of *Am. J. Obst. & Gynec.*)

*B*. Synclitism. Illustrating one concept of the mechanism of engagement. This concept assumes that since the symphysis is short and the sacrum is long the posterior aspects of the head must descend more rapidly than the anterior part. We have not observed this mechanism in any roentgenologic examination. (From Williams, Obstetrics. Published by D. Appleton-Century Co.)

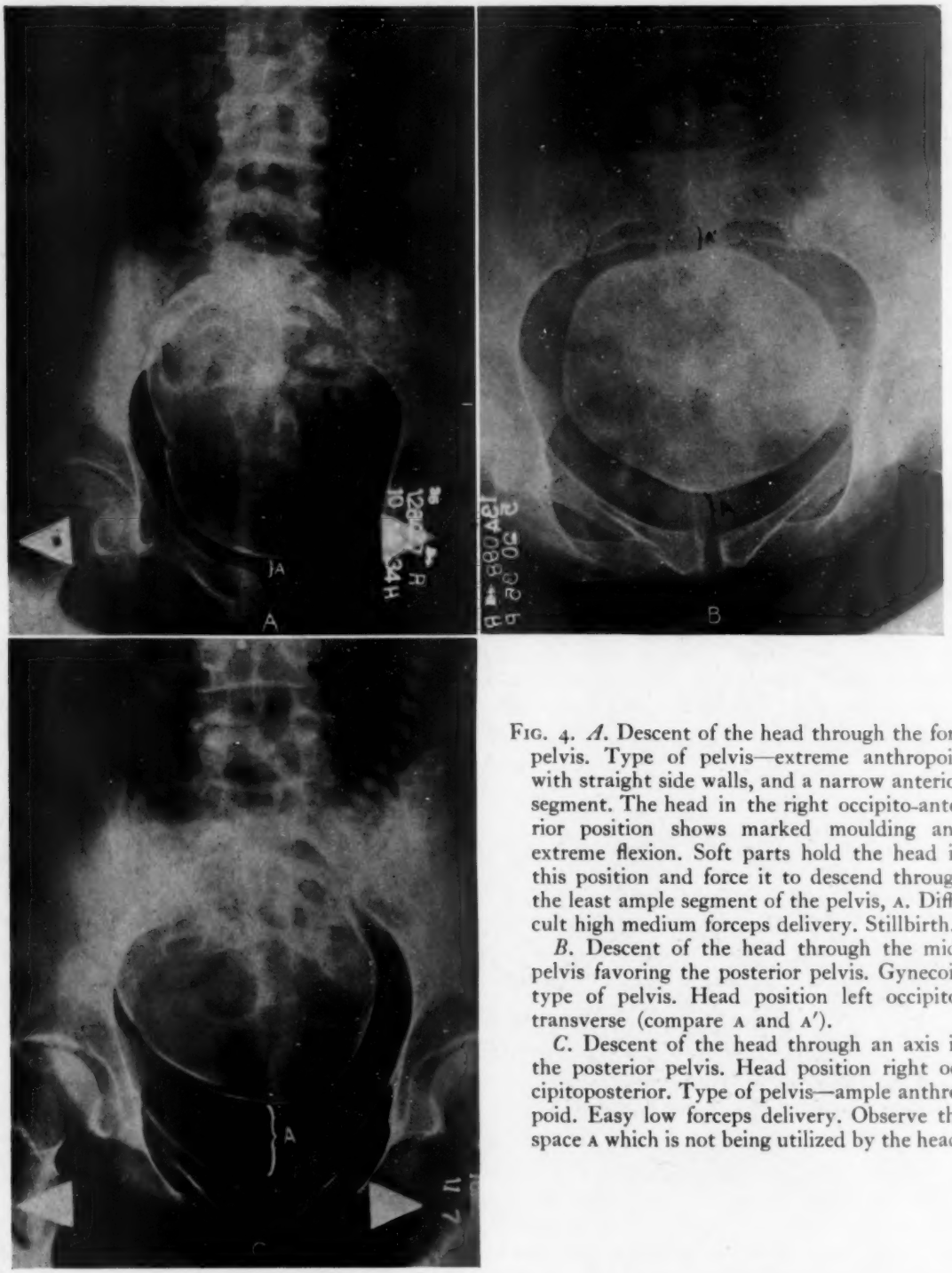


FIG. 4. *A*. Descent of the head through the fore pelvis. Type of pelvis—extreme anthropoid with straight side walls, and a narrow anterior segment. The head in the right occipito-anterior position shows marked moulding and extreme flexion. Soft parts hold the head in this position and force it to descend through the least ample segment of the pelvis, A. Difficult high medium forceps delivery. Stillbirth.

*B*. Descent of the head through the mid-pelvis favoring the posterior pelvis. Gynecoid type of pelvis. Head position left occipito-transverse (compare A and A′).

*C*. Descent of the head through an axis in the posterior pelvis. Head position right occipitoposterior. Type of pelvis—ample anthropoid. Easy low forceps delivery. Observe the space A which is not being utilized by the head.

was utilized early in labor was a favorable prognostic sign because, until this fact was demonstrated, grave doubts were entertained in regard to the advisability of allowing a trial of labor.

It is possible to observe a normal labor in the event of descent through the fore pelvis, but this seems to be the exception rather than the rule. A head which is forced to descend close to the symphysis will en-

counter more bony resistance than would occur with descent through the posterior pelvis, because the anterior segment has less capacity than the posterior segment. In contrast to the efficient mechanism frequently observed with descent through the posterior segment in abnormal pelves, labor is usually prolonged and associated with uterine inertia and slow dilatation of the cervix. A good example of inefficient labor through the anterior segment of an abnormal pelvis is illustrated in Figure 6. The head, forced to descend through a narrow fore pelvis, shows adjustment by rotation in a spiral manner to an anterior position. In this particular example the transverse mechanism illustrated in Figure 5 would have occurred if the head had descended through the posterior pelvis, and labor would have been shorter and easier.

### 3. HEAD ADAPTATION TO PELVIC SHAPE

Since the shape of the anterior segment of the inlet may differ from the shape of the posterior segment, the obstetrical position of the head will be influenced according to the shape of the segment through which it descends. This idea is illustrated diagrammatically in Figure 7. There are, of course, numerous exceptions to this rule, because head size and its reaction to the forces of labor by moulding and flexion may prevent

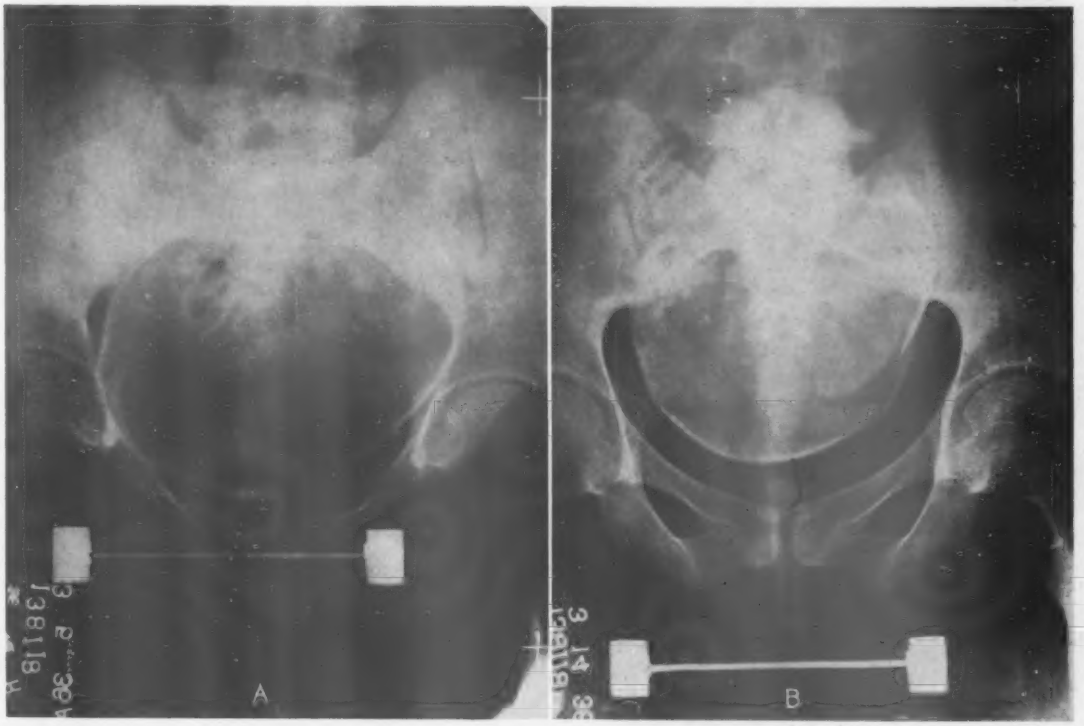


Fig. 5. Efficient labor in an abnormal pelvis. *A*. Chart No. 459627. X-ray No. 138118. A white primipara, aged twenty-one, was delivered of a 3,650 gm. child by low medium forceps from the right occipitoposterior to the right occipitotransverse position after a twenty-three hour labor. Roentgenograms were obtained nine days before delivery. A large narrow type of head is floating above the inlet. Type of pelvis—android flat with straight side walls, narrow subpubic arch, and straight sacrum.

*B*. Same case after onset of labor. The head is well flexed and moulded and is descending through the posterior pelvis as far removed from the symphysis as possible A, right occipitotransverse to right occipitoposterior position. Descent occurred rapidly until arrest occurred with caput bulging the perineum right occipitotransverse position. Barton forceps were used with low rotation after caput was brought in sight by lateral flexion. Refer to lateral view of this pelvis illustrated in Figure 18, *B*, Part II. The straight sacrum with an average inclination allows the head to descend to a low level below the ischial spines because there is an ample posterior sagittal diameter at the level of the spines.

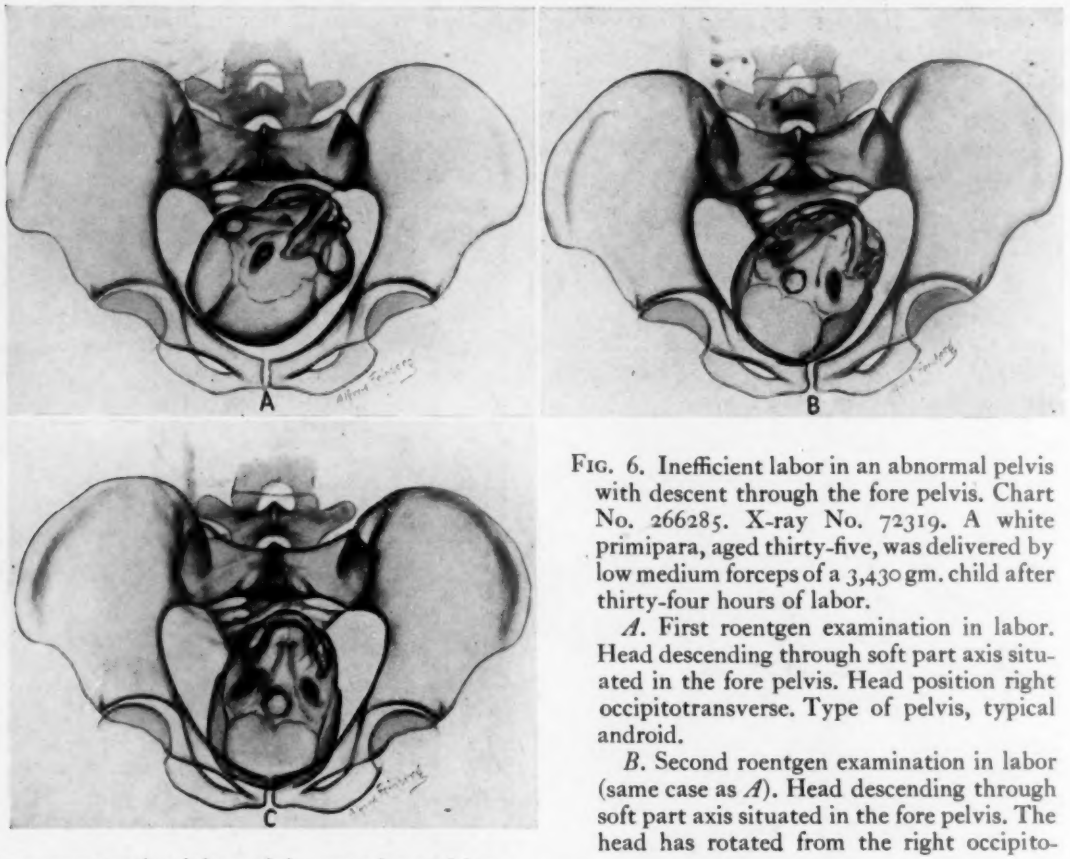


FIG. 6. Inefficient labor in an abnormal pelvis with descent through the fore pelvis. Chart No. 266285. X-ray No. 72319. A white primipara, aged thirty-five, was delivered by low medium forceps of a 3,430 gm. child after thirty-four hours of labor.

*A*. First roentgen examination in labor. Head descending through soft part axis situated in the fore pelvis. Head position right occipitotransverse. Type of pelvis, typical android.

*B*. Second roentgen examination in labor (same case as *A*). Head descending through soft part axis situated in the fore pelvis. The head has rotated from the right occipito-transverse to the right occipito-anterior position.

*C*. Third roentgen examination in labor (same case as *A* and *B*). With further descent through the fore pelvis the head has rotated almost to a direct occipito-anterior position at the level of the spines. Delivery by low medium forceps from this position. (Courtesy of *Am. J. Obst. & Gynec.*)

the expected adaptation. If the long oval shape of the head is substituted for the sphere illustrated in Figure 7 and the inlet is made to correspond to the shapes of the anterior and posterior segments of the four parent types, the position of the head, characteristically associated with each type, can be explained for each axis of de-

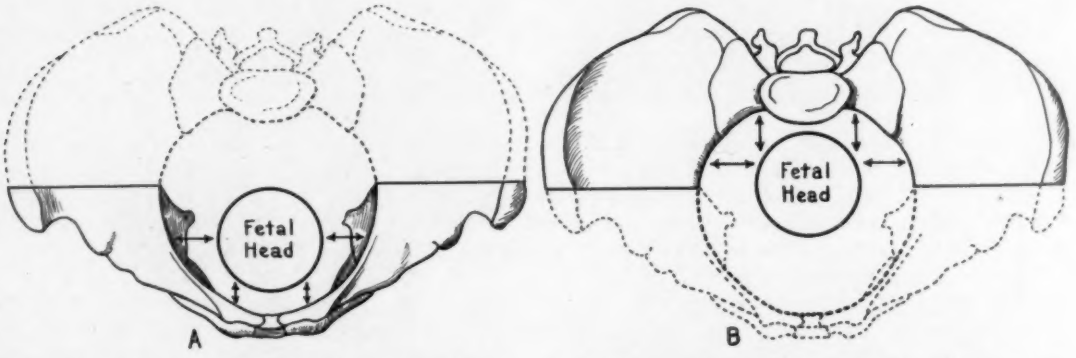


FIG. 7. Principles of head adaptation to pelvic type. *A*, head descending through posterior pelvis will adapt itself to the shape of the posterior segment; *B*, head descending through anterior pelvis adapts itself to shape of the anterior segment. (Courtesy of *Am. J. Obst. & Gynec.*)

scent (Fig. 8). For gynecoid, platypelloid, and android types, the flat straight margin of the sacrum predisposes to a transverse position of the head if it is brought close enough to the sacral region (Fig. 8, *A* and *B*). In the anthropoid types, the transversely narrowed inlet, in association with the sacral concavity, more easily admits the head in the oblique anterior or posterior position (Fig. 8, *C*). In the borderline types of inlet, as revealed in the android-anthropoid type, a transverse position rather than an oblique posterior position may obtain if the head descends close to the sacrum through the posterior pelvis (Fig. 8, *D*). If the head descends through the fore pelvis in this borderline type, the influence of the posterior pelvis is removed and the shape of the anterior segment determines the occurrence of anterior oblique, transverse, or

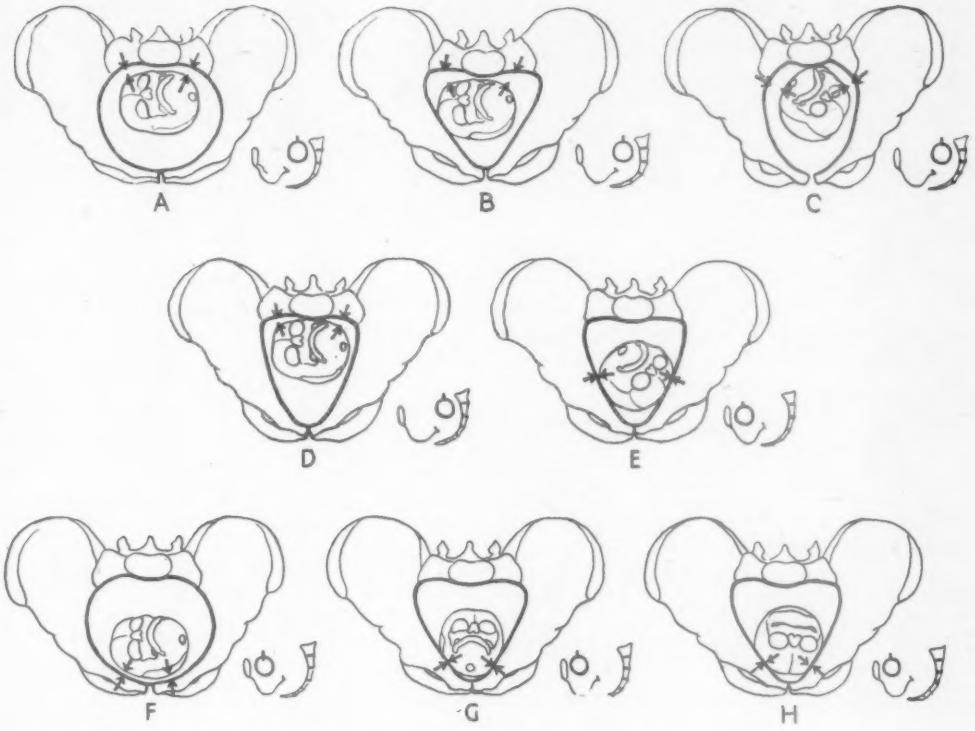


Fig. 8. Adaptation of fetal head to pelvic shape for variable axes of descent.

*A.* Transverse position in gynecoid and platypelloid types caused by the shape of the posterior pelvis as the head descends in an axis through the posterior pelvis.

*B.* Adaptation of head to transverse position in the android type for the same reason.

*C.* Adaptation to the occipitoposterior position or the oblique anterior position in anthropoid type for the same reason.

*D.* Adaptation of the head to the transverse position in the android-anthropoid type as head descends through posterior pelvis due to the flat posterior segment.

*E.* Adaptation of the head to an occipitoposterior position (or anterior position) as the head descends through axis in the fore pelvis in the android-anthropoid type.

*F.* Adaptation of the head to a transverse position with descent through the fore pelvis in pelves possessing a wide angle at the inlet (retropubic angle).

*G.* Adaptation of the head to an anterior position in a narrow fore pelvis when the head descends through the anterior segment.

*H.* Adaptation of the head to a posterior position in a narrow fore pelvis when the head descends through the anterior segment.

As a result of these principles of head adaptation, the obstetrical position of the head after engagement has occurred may be quite different from the position which existed before the onset of labor.

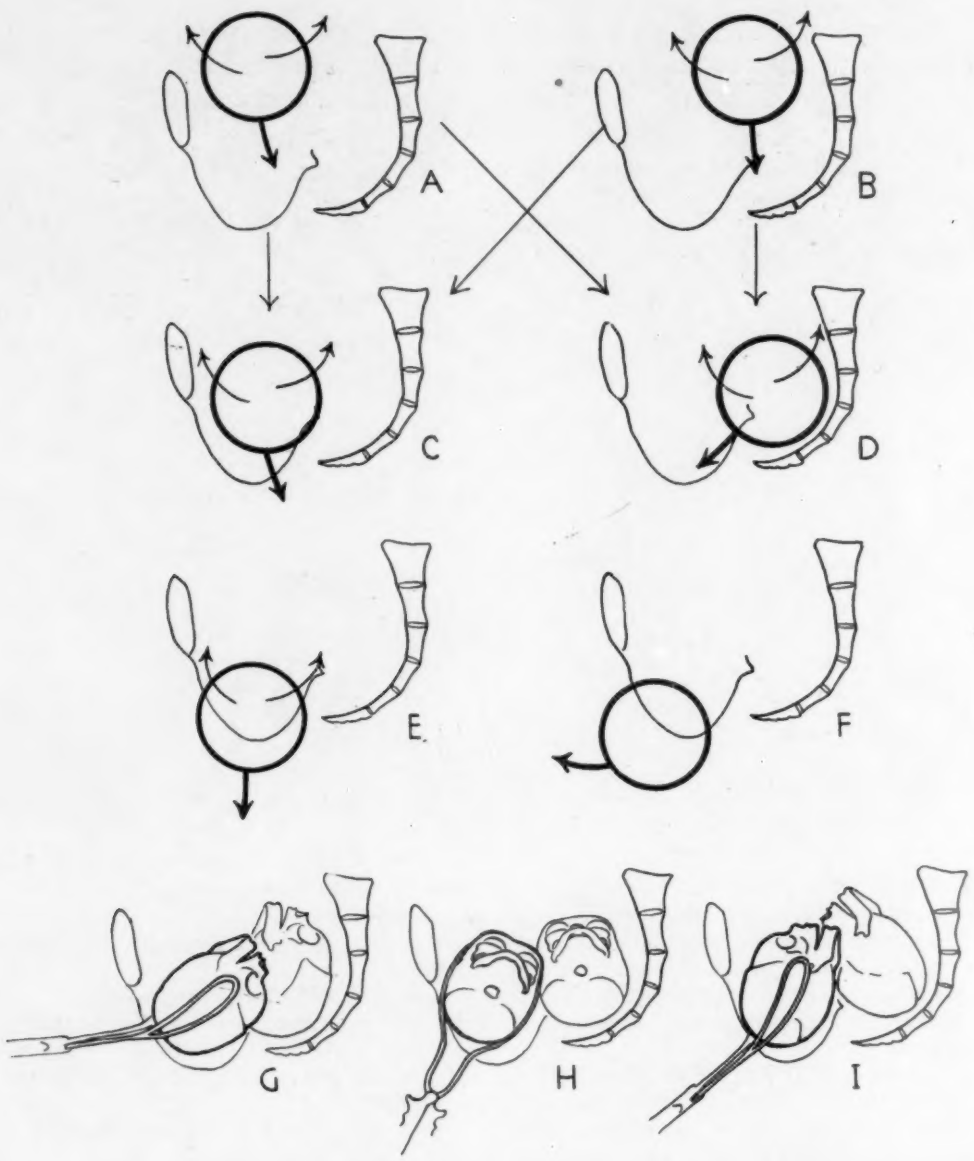


FIG. 9. A diagrammatic attempt to illustrate certain principles to be considered in the use of the obstetrical forceps or in manual methods of assisting labor. It is to be realized that a head in the position illustrated in *A* may descend downward to *C* or downward and backward to the position shown in *D*. The head in *B* may be carried downward to *D* or downward and forward to position shown in *C*. Rotation of the head depends upon the shape of the pelvis at the level of arrest or its shape above or below. A head arrested as in *A* should be deviated downward and backward. A head arrested as in *B* should be brought downward. A head arrested at *C* should be deviated downward and backward away from the symphysis. A head arrested at *D* must be brought downward and forward into the pelvic outlet. A head arrested over the outlet as in *E* should be brought to a lower level downward before the act of extension as in *F*.

In the diagrams shown in *G*, *H*, and *I* an attempt has been made to illustrate how forceps should bring a head forward over the outlet from an arrest in the posterior pelvis as in *D*.

*G*. The act of extension for arrest in anterior oblique position.

*H*. The act of lateral flexion for arrest in transverse position.

*I*. The act of increased flexion for direct occipitoposterior positions. The head becomes flexed as the brow meets the resistance of the anterior portions of the fully dilated cervix or the pubic symphysis.

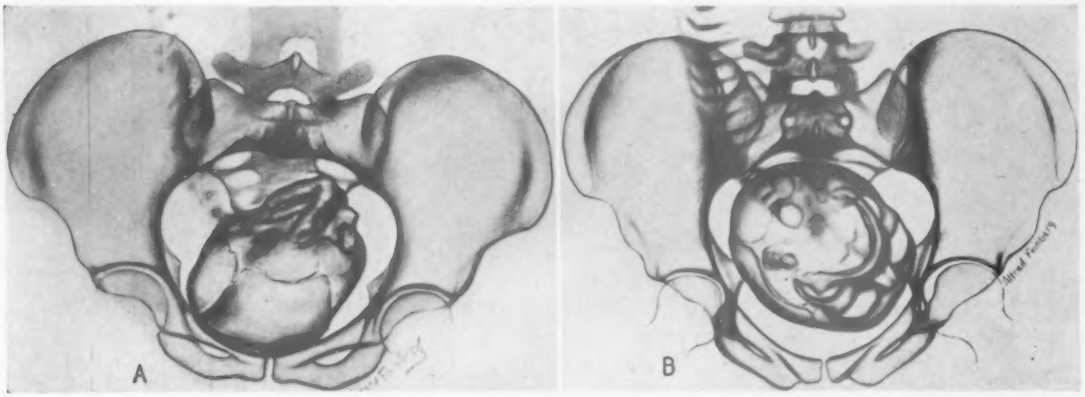


Fig. 10. Descent of the head through the anterior segment in a normal pelvis. *A*. Chart No. 476830. X-ray No. 144308. A white primipara, aged thirty-four, was delivered by low medium forceps of a 3,550 gm. child after a labor of twenty-six hours. Films obtained in labor show a gynecoid type with slight flat characters with the vertex in the right occipitotransverse position held close to the posterior aspect of the symphysis overhanging the posterior pelvis. No disproportion. The cervix at four fingers dilatation was situated in the fore pelvis. The head adapted itself to the occipitotransverse position to conform to the wide angle of the fore pelvis. The head was so close to the pubic rami it was impossible to apply Keiland forceps. Curved forceps were applied with a poor cephalic application. Depression of the forceps handle deviated the head from the inner aspects of the pubic rami.

*B*. Arrest of the head in the right occipitoposterior position behind a narrow interspinous diameter in a normal pelvis. Attempts at manual anterior rotation were unsuccessful until the head was elevated above the conflicting ischial spines.

posterior oblique positions (Fig. 8, *E*). Adjustment of the head to the fore pelvis is shown in Figure 8, *E*, *F*, *G* and *H*.

The study of head position in relation to pelvic type at the onset of labor shows the tendency of the head to engage with its long diameters utilizing the largest pelvic diameters, without consideration of the axis of descent (Table 1).

These principles of head adaptation indicate the importance of pelvic shape in the cause of *deep transverse arrest* and *deep posterior arrest* of the head. Formerly it was supposed that deep transverse arrest of the head occurred during the process of rotation from an original posterior position. The transverse arrest is characteristically associated with the flattened posterior segment of either the gynecoid, platypelloid, or android posterior pelvis. In the event of descent through the fore pelvis, a transverse arrest occasionally is found in a pelvis conforming to any primary type which displays a wide angle behind the symphysis and presents a flat surface to the lateral aspects of the fetal head, bringing about adjustment to the transverse position (Fig. 8, *F*). The arrested posterior position is characteristically associated with the anthropoid type of posterior pelvis when the head descends through the posterior pelvis (Fig. 8, *C*). If the occipitoposterior position occurs with descent through the fore pelvis, the pelvis usually shows a transversely narrowed anterior segment (Fig. 8, *E* and *H*).

Table I

HEAD POSITION AT THE INLET IN RELATION TO PELVIC TYPE AS DETERMINED BY A ROENTGEN EXAMINATION OF 175 PRIMIPARAS EARLY IN LABOR

| | Gynecoid | Android | Anthropoid | Combined |
|---|---|---|---|---|
| Primary posterior oblique | 10% | 20.5% | 28.5% | 18.5% |
| Primary transverse | 69% | 71.0% | 37.5% | 60.0% |
| Primary anterior oblique | 20% | 8.5% | 17.0% | 16.0% |
| Direct occipito-anterior | 1% | — | 17.0% | 5.5% |

In gynecoid and android types, transverse positions occur in approximately 70 per cent of the cases. In anthropoid types there is a marked decrease in the transverse positions and a decided increase in oblique anterior and posterior positions, showing the tendency on the part of the head to utilize the long oval inlet. The android types show an increase in posterior positions and a decrease in anterior oblique positions over the gynecoid type. The narrow fore pelvis of the android type admits the frontal portion of the head in an oblique posterior position to better advantage than the round occipital region.

FIG. 11. The mechanism of labor in platypelloid types. *A*. Chart No. 332773. X-ray No. 97350. A white primipara, aged thirty-five, was delivered by medium forceps of a 4,370 gm. child after a labor of thirty-five hours. Type of pelvis, a wide platypelloid type with straight side walls.

Anteroposterior diameter.....10.5 cm.
Interspinous diameter.....14.0 cm.

Films obtained in labor show the vertex deeply engaged in the right occipitotransverse position. Arrest occurred in this position close to the sacrum low in the posterior pelvis (level *D*, Fig. 9). Barton forceps by lateral flexion brought the head against the pubic rami over the outlet (as in *E*, Fig. 9). With traction, force was misdirected against the pubic rami. A cephalic application was made with Haig Ferguson forceps. It was possible to make traction parallel to the symphysis until the biparietal diameter descended to the level of the plane of the outlet in front of the sacral tip. At this low level anterior rotation was accomplished.

Such information is helpful in predicting the probable mechanism of labor from the roentgenologic study of pelvic shape and fetal-pelvic relationships. Errors in prognosis may occur because it is almost impossible to determine, before the onset of labor, whether the head will descend through the anterior or posterior pelvis; the latter, however, is more common. The position of the partially dilated cervix may suggest the axis of descent which will take place through the lower pelvis. If the cervical opening is located at or behind the spines, the head, in all probability, will descend through the posterior pelvis. If, on the other hand, it is located in front of the spines, the head is likely to descend through the fore pelvis. It is of great importance to realize that either mechanism may occur. The roentgenologist should recognize the one or the other from the study of the fetal-pelvic relationships in the stereoscope, while the obstetrician should identify correctly the same relationships from vaginal examination.

#### 4. THE SIGNIFICANCE OF PELVIC SHAPE IN THE TREATMENT OF PELVIC ARREST

In the preceding text an effort has been made to point out the variations in the axis of descent and the rôle of pelvic shape in determining the obstetrical position of the head. Knowledge of these two factors is important in the management of labor and in the treatment of pelvic arrest. As soon as the roentgenologist has obtained sufficient experience in film interpretation to appreciate pelvic type and the fetal-pelvic relationships during labor, practical suggestions may be offered in regard to axis of traction, the proper level for anterior rotation of the head, and the optimum mechanism through the lower pelvis. During the past eighteen months the attending and resident staff of the Sloane Hospital for Women have made a definite attempt to apply this information. The result has been a decrease in the incidence of difficult forceps deliveries by means of more careful selection of cases for caesarean section; yet the incidence of the latter operation has not increased. Forceps operations have been handled on better mechanical principles and with a decrease in fetal mortality because there has been a more accurate knowledge of the shape of the pelvis and of the position of the head. Although by a study of the roentgenograms taken before labor it may be possible to predict the type of labor which will ensue in certain cases, the many factors involved make the films taken during labor much more valuable.

It is, however, difficult to explain by means of diagrams or description the man-

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*B.* Lateral view of the same case. The head in the occipitotransverse position is low in the pelvis with its long axis parallel to the sacrum (anterior parietal tendency). The length of the posterior sagittal diameter at the level of the spines allowed this low descent. Arrest of the head was caused by the forward sacrococcygeal platform in association with the flat type of pelvis which prevented anterior rotation. Observe the short anteroposterior diameter in front of the sacral tip through which the head was made to descend in the occipitotransverse position before anterior rotation could occur.

*C.* Chart No. 320649. X-ray No. 89937. Anterior rotation of the head arrested in the occipitotransverse position in a platypelloid pelvis is mechanically wrong. Separation of the symphysis and a stillbirth may result if such attempts are forcibly made above the level of the outlet as occurred in this case. Second delivery was by caesarean section.

*D.* Chart No. 450439. X-ray No. 133362. A white multipara, aged thirty, whose first child was delivered by difficult forceps. Child living. The second child whose weight at birth was 4,060 gm. was delivered by low forceps from the left occipito-anterior position after a labor of thirteen hours. The inlet conforms to the extreme platypelloid type. Films obtained in labor show the head engaging in the left occipito-anterior position. Disproportion at the inlet is 200 cc. as estimated by comparison of the volume of the head and the volume of the anteroposterior diameter inlet. Biparietal diameter of the head equals 10 cm.

Anteroposterior diameter of inlet..... 9.0 cm.
Transverse diameter of inlet.....14.5 cm.

The head engaged in the left occipito-anterior position so the biparietal diameter of the head could utilize the more ample oblique diameter of the inlet.

ner in which the information obtained from a study of the roentgenograms may be applied clinically. Careful study of Figure 9 will show *how* the head should be made to descend to lower levels if arrest occurs in the fore pelvis or in the posterior pelvis. In this diagram, the fetal head is indicated intentionally as a sphere because the principles obtain for all obstetrical positions of the head. The following case studies grouped according to pelvic type have been selected to show in detail the practical application of the points illustrated diagrammatically in Figure 9.

*The Gynecoid Type.* The spontaneous birth of an average-sized child in eighteen hours or under is commonly associated with a large anthropoid-gynecoid type of pelvis. Operative interference is rarely necessary in this normal group. The axis of descent is usually through the midpelvis, favoring the posterior pelvis. Occasionally the head descends through the fore pelvis, in which event operative interference may become necessary (Fig. 10, *A*). In normal pelves a narrow interspinous diameter may cause an occipitoposterior position if the occiput should rotate behind the ischial spines into the hollow of the sacrum (Fig. 10, *B*).

*The Platypelloid Pelvis.* In platypelloid pelves a *transversely arrested head, as a rule, cannot be rotated manually* because of its proximity to the sacrum behind and to the symphysis in front. Accordingly, *the head must be brought to a lower level in the pelvis in the transverse position* and forward by so-called lateral flexion so that anterior rotation can be accomplished with caput in sight (Fig. 11, *A* and *B*). Forceful attempts at rotation at the level of the spines may result in serious injury to mother and child, as occurred in the example shown in Figure 11, *C*. In flat pelves it may be difficult to obtain a true cephalic forceps application, even though it is desirable. Under such circumstances, a pelvic application of the forceps to occiput and face may be the only means of delivery, unless version and breech extraction is deemed advisable. In true flat pelves the ischial spines and tuberosities as a rule cause no difficulty, as there is ample transverse space throughout the pelvis. Occasionally we have seen cases of platypelloid pelves in which the oblique diameters were slightly larger than the anteroposterior so that the fetal head came down in the oblique diameter. Stude and Scherman[3] have drawn attention to engagement in flat pelves in the anterior oblique positions (Fig. 11, *D*). We have ob served several examples of this method of adaptation. The head adjusts itself in this position in the upper pelvis so that the widest biparietal diameter can make use of the longer oblique pelvic diameter. For the same reason, engagement in the posterior oblique position may occur.

*The Android Type.* If the head enters the inlet through the posterior pelvis, it undergoes an adjustment to the transverse position (Fig. 12, *A* and *B*). Accordingly, *the head may tend to maintain a transverse position to a lower level.* Attempts at anterior rotation are usually unsuccessful because this movement is opposed by the flat posterior pelvis against which the lateral side of the head impinges. Descent, as a rule, continues with the head in the transverse position until the bottom of the posterior pelvis or three-point landing is reached (the concavity formed by the ischial spines and the sacrococcygeal platform). Rotation begins at this low level but, if the upper sacral region still opposes the frontal region of the head, *lateral flexion* (Fig. 12, *C*) into the fore pelvis takes place until the head is sufficiently displaced from the sacrum to enable the frontal region to rotate under the promontory into the hollow of the sacrum (Fig. 12, *D*). Rotation, under such circumstances, takes place on the inner aspect of the pubic rami, but at a low level with caput in sight. If forceps are applied, care must be taken to allow the head to follow this mechanism.

If the side walls of the pelvis are straight and the subpubic arch is wide, lateral flexion of the head in the transverse position with forceps enables the head to descend to

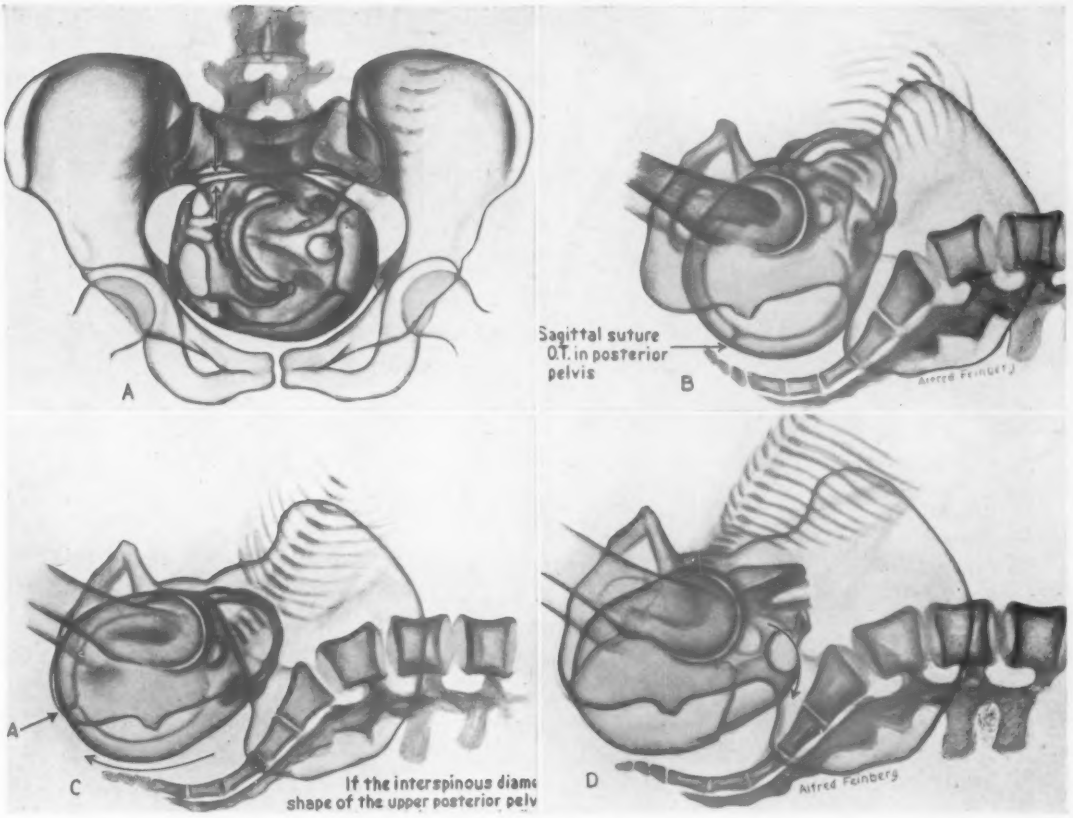


Fig. 12. The normal mechanism in android types. *A*. The normal mechanism in android types (occipitotransverse position maintained to a low level). Inlet view: rotation from the occipitotransverse position to an oblique anterior position does not occur on account of the opposing forces between the temporal region of the head and the lateral aspects of the sacral region at the inlet (see arrows).

*B*. Normal mechanism in android types. Lateral view of *A*. Vertex in occipitotransverse position at bottom of posterior pelvis close to lower sacral region.

*C*. Normal mechanism in android types. Lateral view. If the side walls of the pelvis are straight and the interspinous diameters wide, the occipitotransverse position persists (for reasons illustrated in *A*). For descent to occur the head demonstrates "anterior lateral flexion" between contractions as it descends in the fore pelvis. This means that the median sagittal suture moves more and more in front of the ischial spines and downward.

*D*. Normal mechanism in android types. Lateral view. Anterior spiral rotation from the occipitotransverse position occurs at such a low level in the lower fore pelvis that the fetal brow may move without resistance under the promontory. (Courtesy of *Am. J. Obst. & Gynec.*)

a lower level in the same position (Fig. 13, *A*). In the case of a transverse arrest associated with converging side walls and a narrowed interspinous diameter, it is mechanically wrong to deliver the head to a lower level in the same position. It is important to effect at least an anterior oblique position before traction is attempted or serious soft part injury will result as the head is brought into contact with the ischial spines (Fig. 13, *B* and *C*). Occasionally an android type which is flat at the inlet and has converging side walls will be encountered. In such types anterior rotation is advisable, if possible, before attempting traction. A good example of the anterior spiral rotation with descent in the narrow fore pelvis of an android type of pelvis has been illustrated in Figure 6. Transverse arrest in the fore pelvis of an android type with a gynecoid anterior segment is illustrated in Figure 13, *D*. The lateral aspects

FIG. 13. Mechanism in android types. *A*. Chart No. 429806. X-ray No. 126116. A white primipara, aged twenty-seven, was delivered by medium forceps of a 3,220 gm. child after a labor of twenty-seven hours.

Anteroposterior diameter of inlet.....10.5 cm.
Widest transverse diameter of inlet.....13.0 cm.
Interspinous diameter.....10.5 cm.

Type of pelvis, typical android with straight side walls and a moderate subpubic arch. Films in labor show the vertex descending through the posterior pelvis right occipitotransverse position. The head arrested just below the ischial spines. Barton forceps applied. Attempts at anterior rotation unsuccessful due to the shape of posterior pelvis. With strong traction, the head descended to a low level in the right occipitotransverse position. Rotation to an anterior position was affected with caput in sight. (Classical mechanism for an android pelvis with straight side walls and ample outlet.)

*B*. Chart No. 430921. X-ray No. 125938. A white primipara, aged thirty-nine, was delivered by low forceps of a 3,690 gm. child after a labor of forty-nine hours.

of the head conformed to the flat anterior boundary of the fore pelvis so closely that attempts at manual rotation were unsuccessful. Barton forceps succeeded in deviating the head downward and backward and the head descended with slight traction to a lower level in the transverse position. Low anterior rotation was easily accomplished with caput in sight.

*The Android-Anthropoid Type.* The android-anthropoid type introduces the bad feature of both the android and anthropoid pelves. In the first example (Fig. 14, *A*) the patient went into labor without a roentgen examination. The head was arrested at the level of the spines in the transverse position. A difficult median forceps operation was done. Manual rotation was difficult and was completed to an anterior oblique position by the use of Barton forceps before attempting traction. From this anterior position the head was delivered through the lower fore pelvis by pelvic curved forceps. Although good mechanical principles were used in the delivery, the child was larger than average (3,799 gm.) and a stillbirth resulted. Roentgen examination after delivery showed a small android-anthropoid pelvis with converging side walls and a narrow interspinous diameter. The head was arrested at the level of the spines in the transverse position because the axis of descent apparently carried the head through the posterior pelvis and necessitated the transverse adjustment to the flat android shape of the posterior segment according to the principles shown in Figure 8, *D*. Further descent in the transverse position was not advisable because of the narrow interspinous diameter. Anterior rotation of the head at the level of arrest made possible the use of the long anteroposterior diameters through the lower pelvis. This case illustrates the value of a roentgenologic examination during labor. If the abnormal pelvis and the large head had been recognized early in labor, a caesarean section would have been indicated.

In android types with anthropoid characteristics, posterior positions are also common. In order to assume the occipitoposterior position, the head must descend through the center of the pelvis until the influence of the flat posterior pelvis is

Anteroposterior diameter of inlet.....10.5 cm.
Widest transverse diameter of inlet.....13.0 cm.
Interspinous diameter.....10.5 cm.

Type of pelvis, android with ample anteroposterior length, straight side walls with a *narrow* subpubic arch (see Fig. 14, Part II). Films obtained in labor show the vertex left occipitotransverse at level of midpelvis. Head slowly descended and rotated to a left occipito-anterior position. The ample anteroposterior diameters and straight side walls allowed anterior rotation in spite of the android shape of the posterior pelvis and the narrow subpubic arch.

*C.* Chart No. 431761. X-ray No. 136007. A white primipara, aged twenty-eight, was delivered by difficult medium forceps of a 3,550 gm. child after thirty-four hours of labor. Films obtained in labor show the vertex in midpelvis in the left occipitotransverse position descending through the posterior pelvis just above the narrow interspinous diameter. The pelvis conforms to the android type slightly flat with a narrow interspinous diameter and converging side walls. The head could not be rotated with Barton forceps nor was it desirable to bring the head to a lower level in the occipitotransverse position because of the narrow interspinous diameter. Delivery was finally accomplished by use of a pelvic curved forceps applied in poor cephalic application to the left occipito-anterior position. The anterior spiral descent is necessary to avoid the narrow spines. Deep sulcus lacerations occurred. The child was badly shocked but was discharged living.

*D.* Chart No. 494106. X-ray No. 155309. A white primipara, aged nineteen, was delivered by medium forceps of a 3,950 gm. child after twenty-one hours of labor. Films obtained in labor show a typical ample android-gynecoid type of pelvis with a wide flat angle behind the symphysis, straight side walls, and a wide subpubic arch. The head, descending through the anterior segment, was arrested in the left occipitotransverse position close to the descending pubic rami. Barton forceps were applied. By deviating the head away from the symphysis, traction brought it to a lower level in the left occipitotransverse position through the fore pelvis before anterior rotation could be accomplished. The shape of the fore pelvis aided in causing the left occipitotransverse position (see also Fig. 8, *F*).

FIG. 14. The mechanism in the android-anthropoid type. *A*. Chart No. 526644. X-ray No. 164119. A white primipara, aged thirty-one, was delivered of a 3,799 gm. child, stillborn due to a difficult medium forceps delivery after thirty-one hours of labor. Films obtained after delivery show a very typical small android-anthropoid type with converging side walls and a narrow interspinous diameter. Arrest occurred slightly below the spines in the left occipitotransverse position (see Fig. 8, *D*, and text). Rotation was effected at the level of arrest with considerable difficulty by Barton forceps after which pelvic curved forceps were applied and the head delivered with strong traction from the anterior oblique position. This case illustrates the need for anterior rotation in the presence of a narrow fore pelvis at lower levels. The error in judgment existed in allowing delivery through this small abnormal pelvis.

*B*. Chart No. 437171. X-ray No. 133338. A white primipara, aged twenty, was delivered of a 2,930 gm. child by low forceps after twenty-three hours of labor. Films obtained in labor showed the head deep in the fore pelvis, well flexed, in the direct occipitoposterior position with the brow close to the symphysis. Pelvis type, android-anthropoid with a narrow fore pelvis. With caput on perineum, the head was elevated to a higher level and an easy manual rotation to the anterior position performed. The head descended to be delivered by an easy low forceps. This shows adaptation to the narrow fore pelvis to the occipitoposterior position as the head descends through the anterior segment (see Fig. 8, *E*).

passed and the narrow frontal diameter of the head is permitted to coincide with the narrow angle of the fore pelvis (Fig. 8, *E*, and Fig. 14, *B*). In this event, the occipital portion of the head has sufficient space to lie in the posterior oblique position in spite of the shape of the posterior pelvis. Because of the proximity of the brow to the posterior aspects of the symphysis, the head is usually well flexed and moulded so that manual rotation can be easily accomplished after elevation of the head due to the space available in the posterior pelvis. The anthropoid type of pelvis is peculiarly suited for version and breech extraction because the aftercoming head usually adjusts itself in an optimum manner to the long anteroposterior diameter. In our clinic, however, it is rarely used as a method of delivery of the arrested occipitoposterior position.

*The Anthropoid Type.* The treatment of the occipitoposterior position in case of arrest is a favorite obstetrical subject for discussion. In a high percentage of cases the arrested posterior position below the midpelvis will be found in a pelvis with a relatively long anteroposterior diameter complicated by a variety of factors in the lower pelvis, such as a deep true pelvis, converg-

ing side walls and sharp spines, a narrow fore pelvis from inlet to outlet, or a forward lower sacrum.

The four examples shown in Figure 15 will suffice to illustrate the principles of treatment and the complications. The type of pelvis in Figure 15, *A*, is a characteristic anthropoid with a long anteroposterior diameter and definite transverse narrowing, but with straight side walls and a moderate to wide subpubic arch. The fetal head in an oblique occipitoposterior position is not well flexed and there is no disproportion. This case was handled by an easy Scanzoni rotation by forceps because no marked narrowing existed in the lower pelvis at the outlet.

The pelvis in Figure 15, *B*, is also characteristically anthropoid, but, in addition there is convergence of the side walls, prominent spines, a deep true pelvis, and a narrow subpubic arch. The sacrum has a good concavity and a backward inclination. Arrest occurred at the level of the spines. Manual rotation was unsuccessful. Forceps were applied to the direct occipitoposterior position; with gentle traction the head descended to the outlet and rotation was effected with the caput in sight at the vulva. We have similar examples of this particular type of anthropoid pelvis, in which the delivery has been accomplished by version and breech extraction or elevation of the head to the inlet and easy manual rotation, both procedures being recognized as based on sound mechanical principles.

The third example (Fig. 15, *C*) also conforms to a well-formed anthropoid type of pelvis. In this instance delivery was effected by poor mechanical principles. The head was arrested in the low midpelvis in the occipitoposterior position and was rotated to a transverse position in spite of the narrow transverse diameter. A cephalic application of the forceps was used in the transverse position, and with traction the head was brought to a lower level in the outlet before anterior rotation was accomplished. The child survived, but it was badly shocked and the parietal bones were fractured. This example illustrates the point that either the rotation of the head to an anterior position must be completed or it must be left in the original occipitoposterior position, because it is mechanically wrong to deliver a head with the longest axis coinciding with the smallest pelvic diameter. In the example shown in Figure 15, *D*, the head was brought down in the transverse position by forceps, and the result was separation of the symphysis and a stillbirth.

Upon recognizing a posterior position which is just posterior to a transverse position (occipitotransverse to occipitoposterior), the obstetrician should be certain of the type of pelvis, because the mechanism of the forceps delivery is largely dependent upon the basic pelvic type. Posterior positions of this minor degree may occur in the android and platypelloid types as well as in typical anthropoid types. With android and platypelloid types, the head should be manually rotated to a transverse position, forceps applied, and the head brought to lower levels in the transverse position. If, however, the pelvis conforms to the anthropoid type, it may not be advisable to cause descent in the transverse position to lower levels unless the transverse diameters are wide.

### 5. The Rôle of the Shape of the Outlet in Operative Deliveries

If the pelvis is adequate enough to allow the head to descend to the pelvic outlet, we have found no case in which the bony abnormality at the outlet was marked enough to prohibit the birth of the child with safety. Numerous examples have been observed, however, in which a knowledge of pelvic shape at this level has simplified the mechanism of delivery. The shape of the outlet in front of the tip of the sacrum may conform to the long oval, the round, the flat, or the wedge-shaped type (Fig. 19, Part II). An excellent example illustrating the mechanism in a flat outlet associated with a flat inlet type is shown in Figure

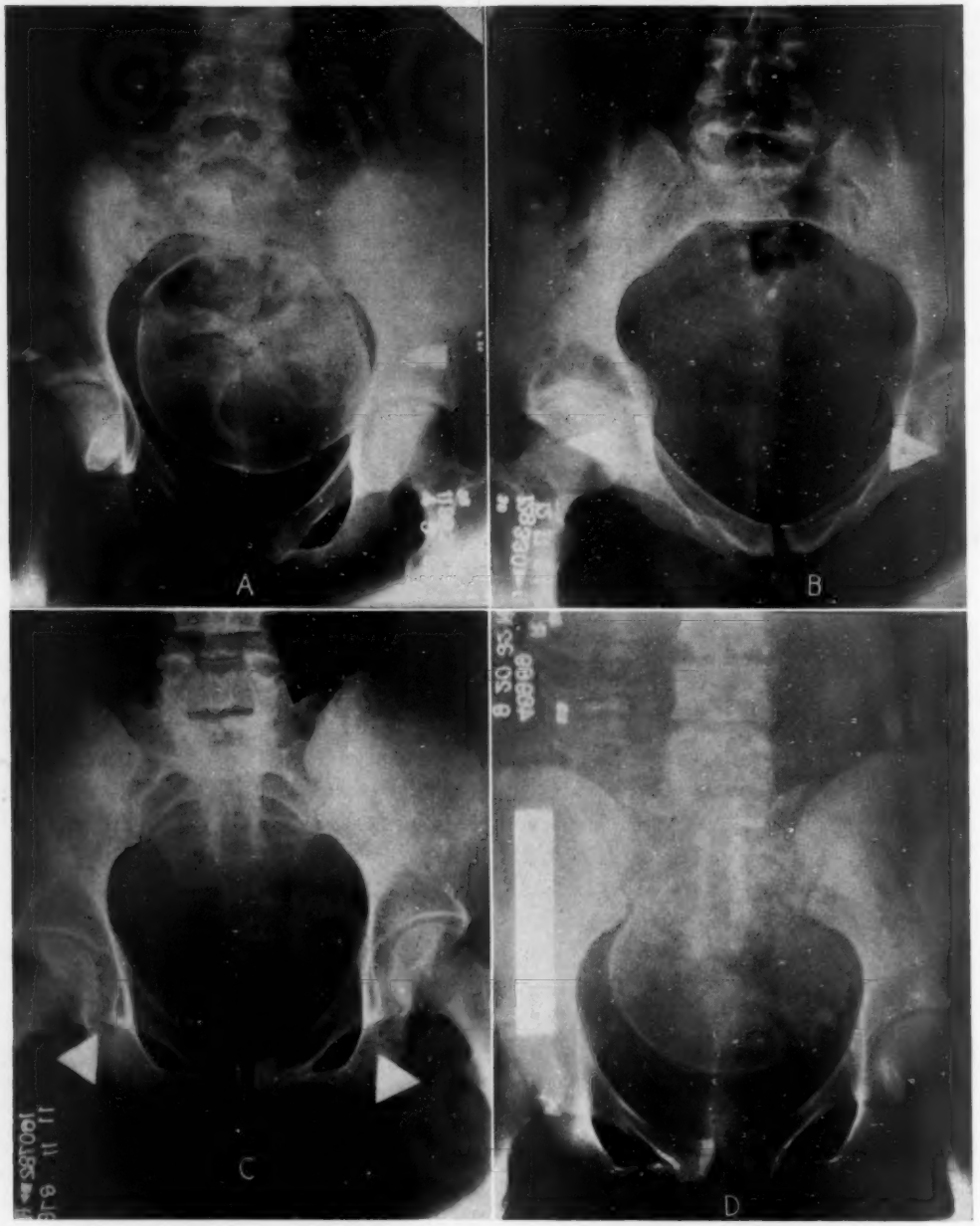


FIG. 15. The mechanism in the anthropoid type. *A*. Chart No. 406457. X-ray No. 119924. A colored primipara, aged nineteen, was delivered of a 2,980 gm. child by medium forceps after twelve hours of labor. Films obtained in labor show a large anthropoid type of pelvis with a narrow fore pelvis behind the symphysis but with straight side walls and an ample subpubic arch. The vertex is deeply engaged in the left occipitoposterior position utilizing the posterior pelvis. Transverse diameters in this region are ample. No progress after full dilatation. An easy Scanzoni maneuver was performed presumably as a result of the small child and the ample transverse diameters in the posterior pelvis. The patient has subsequently delivered a 3,700 gm. child normally. This case illustrates one recognized method of treatment of the occipitoposterior position. Since there is no disproportion, other methods such as manual rotation could have been employed along with a longer trial of labor before attempting delivery.

*B*. Chart No. 418106. X-ray No. 128330. A white primipara, aged twenty-seven, was delivered by medium forceps of a 3,860 gm. child after twenty-one hours of labor. Films obtained after delivery show a characteristic anthropoid type of pelvis with definite transverse narrowing in the form of a narrow

11, *A* and *B*. The head was arrested in the transverse position at the bottom of the posterior pelvis (position *D*, Fig. 9). It was carried by lateral flexion into the fore pelvis over the pelvic outlet, as in position *E*, Figure 9. Before anterior rotation could be accomplished, the head was made to descend in the transverse position by traction parallel to the symphysis until the biparietal diameter passed in front of the sacral tip.

The case studies illustrated in Figure 16, *A* and *B*, also reveal the influence of a flat outlet occurring in pelves with ample space at the inlet, one pelvis conforming to the large anthropoid type, the other to the anthropoid-gynecoid type. The flat shape of the outlet in these cases is caused by a forward sacral tip. In the example shown in Figure 16, *A*, the head is arrested in the occipitotransverse position on the sacral tip low in a large anthropoid type of pelvis. The sacral tip swings forward almost to the plane of the ischial spines. The side walls of the pelvis are straight, and the intertuberous diameter is wide. Hence a flat oval shape is formed at the outlet. It was necessary to deliver the head in a transverse position through the outlet in front of the sacral tip in spite of the ample space above the level of the outlet. In the example shown in Figure 16, *B*, undoubtedly it was possible to deliver the child safely from the anterior oblique position. However, when advancement failed to occur with a trial traction on the forceps handles from the anterior oblique position, the flat shape of the outlet was appreciated. The head was rotated to the transverse position and with the first attempt at traction the head easily passed the sacral tip to be rotated to the anterior position without difficulty at a lower level.

The cases in Figure 16, *C* and *D*, illustrate the influence of the long oval type of outlet which, in one case, is made shorter than the long oval present at the inlet by a forward inclination to the sacrum and, in the other, is accentuated by converging side walls. In the example shown in Figure 16, *C*, a large child was delivered in the occipitoposterior position with strong trac-

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angle behind the symphysis and moderate convergence of the side walls. The sacrum has a backward inclination with a good concavity. Arrest occurred just below the spines in the right occipitoposterior position. Manual rotation was unsuccessful. Attempted forceps rotation was unsuccessful. Simpson forceps were applied to the head in the occipitoposterior position and with moderate traction, the head descended to the outlet in the occipitoposterior position. Easy anterior rotation at this low level occurred. Good mechanics used with a good result.

*C.* Chart No. 300125. X-ray No. 160792. A colored primipara, aged twenty-three, was delivered of a 3,610 gm. child by medium forceps after fourteen hours of labor. Films obtained after delivery show a typical well-formed anthropoid type of pelvis with definite transverse narrowing and straight side walls and a wide subpubic arch. Arrest in the left occipitoposterior position occurred at the level of the spines. Poor mechanics used in delivery. Manual rotation at level of arrest unsuccessful. Barton forceps applied and rotation attempted without success. Simpson forceps applied in a transverse cephalic application without advancement. A Scanzoni maneuver was attempted and the head was brought down to the pelvic floor and rotated with moderate force. Child shocked but survived with multiple fracture of parietal bone. It is mechanically wrong to bring the head to lower levels in the occipitotransverse position in an anthropoid type of pelvis.

*D.* Chart No. 76646. X-ray No. 46969. A colored primipara, aged twenty-seven, was delivered of a 3,500 gm. child by medium forceps after twenty-one hours of labor. Films obtained after delivery (during second pregnancy) showed a typical anthropoid pelvis with straight side walls and a wide subpubic arch. Note the separated symphysis. Head reported arrested at the level of the spines in the left occipitotransverse (?) position. Attempt at manual rotation was unsuccessful. Barton forceps applied and the head rotated to a left occipito-anterior position and pulled down to the pelvic floor. Delivery completed by Simpson forceps. Child died five days later from intracranial hemorrhage. In spite of the reported occipitotransverse arrest, this was probably an original occipitoposterior arrest which was converted into a transverse position and delivered to lower levels in this position resulting in a separation of the symphysis and a stillbirth. A subsequent delivery was normal.

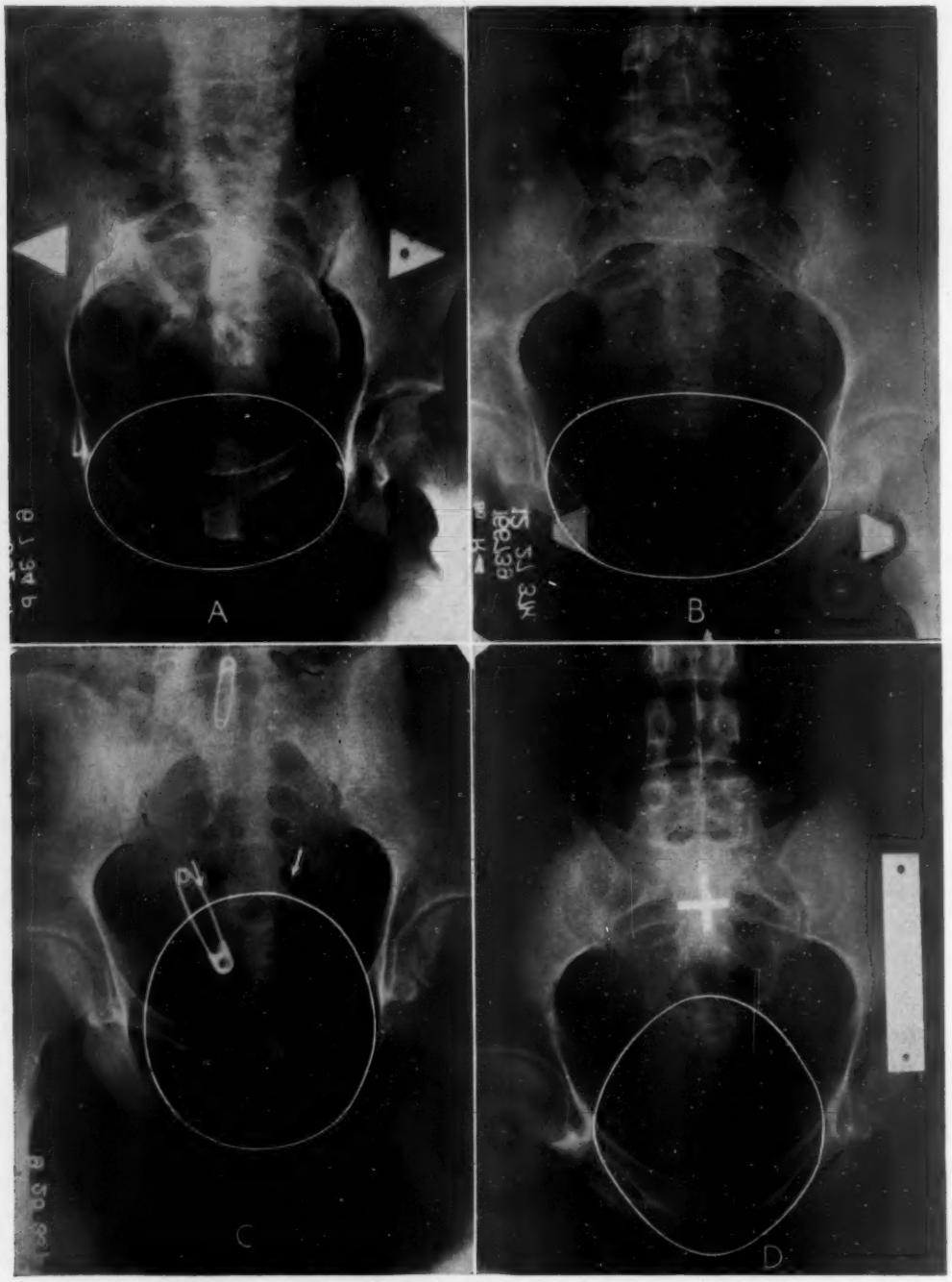


FIG. 16. The mechanism of labor as modified by variations in the shape of the outlet. *A*. Chart No. 419575. X-ray No. 122652. A white primipara, aged twenty-eight, was delivered of a 3,890 gm. child by low medium forceps after twenty-one hours of labor. Films obtained in labor show the vertex arrested low in the pelvis in the left occipitotransverse position. Pelvis a large anthropoid type with straight side walls and a wide subpubic arch. The sacrum with a marked concavity curves forward at a low level to the region of the spines causing a transverse oval shape in front of the sacral tip. To utilize this space, Barton forceps were applied and the head brought to a lower level in the occipitotransverse position before effecting anterior rotation.

*B*. Chart No. 538081. X-ray No. 166739. A white primipara aged twenty-three, was delivered of a 3,780 gm. child by low medium forceps after fifteen hours of labor. Films obtained after delivery show a

tion. The pelvis at the inlet conformed to the anthropoid type. The sacrum had a forward inclination. The shape of the outlet conformed to a small long oval type. A fracture occurred in the sacrum between the fourth and fifth segment. If the shape of the outlet had been appreciated, the obstetrician would not have attempted traction until the head had been rotated to an anterior position. By convergence of the side walls, the outlet in the case shown in Figure 16, *D*, changes to a narrower long oval than existed at the inlet. The pelvis conforms to the android-anthropoid type. The head, arrested in the occipitoposterior position, could not be rotated. The head was delivered in the occipitoposterior position through the long narrow oval outlet similar to the mechanism described for Figure 15, *B*.

In the event of arrest of the head at the level of the bony outlet, pelvic shape is sufficiently important to warrant a determination of its form by vaginal examination before attempting the delivery of the child.

## SUMMARY

In a series of three papers, a review of the roentgen methods of study of the female pelvis and the fetal head as an aid to obstetrical prognosis has been presented. The objectives of roentgen examination are two: to determine (1) whether the bony pelvis is large enough to permit the fetal head to descend safely, and (2) *how* it may descend provided the pelvis is large enough to receive it. Opinions differ as to the importance of these two objectives. Some workers believe the first to be more important and consequently make use of procedures which give accurate measurements of the pelvis and fetal head. The diameters of the bony pelvis are more easily obtained by roentgen methods than are the cephalic diameters. The volumetric method proposed by Ball seems to place the estimation of head size upon an accurate basis. The sizes of the pelvis and the head being determined however, in many cases a prognosis as to ease or difficulty of labor cannot be made with reasonable assurance for several reasons. The ability of the head to flex and mould with efficient uterine contractions and so to overcome even a major degree of disproportion cannot be estimated. Errors in prognosis may occur through the use of the smallest pelvic diameter as the index of pelvic capacity. In a few pelves, depending upon their shape, the smallest diameter *is*

large ample pelvis with straight side walls and a wide subpubic arch, but with a forward lower sacrum which causes a flat type of outlet. Arrest occurred in the forward sacral tip in the left occipitoposterior position, manual rotation to the left occipito-anterior position. Simpson forceps applied. No advance with gentle traction. The head was rotated to a left occipitotransverse position by the forceps and easy descent in that position occurred with gentle traction. Low anterior rotation after the head had passed the sacral tip.

*C.* Chart No. 73584. X-ray No. 45004. A white primipara, aged eighteen, was delivered by a difficult low forceps of a 4,000 gm. child after eighteen hours of labor. Films obtained after delivery showed a large anthropoid type with a forward sacrum which decreased the long oval at the inlet to a less ample oval at the outlet. The head was arrested at the outlet with caput showing. The obstetrician applied forceps to the direct occipito-anterior position and delivered the child by strong traction in the direct occipitoposterior position (error in diagnosis of head position). Child was moderately shocked but survived. The lower sacrum was fractured at points indicated. The head should have been pushed to a higher level and rotated to an anterior position before attempting traction. This patient has had two subsequent normal deliveries.

*D.* Chart No. 355117. X-ray No. 101875. A white primipara, aged twenty-one, was delivered by medium forceps of a 2,390 gm. child after nine hours of labor. Films obtained after delivery show a typical android-anthropoid type with converging side walls, prominent spines. The long oval shape at the inlet is converted into a narrower long oval at the outlet by the converging side walls. Arrest occurred at the level of the spines in the right occipitoposterior position. Without attempts at anterior rotation, the head was brought to a lower level in the direct occipitoposterior position and rotated at a low level with caput in sight. This patient has had a subsequent normal delivery of a 3,250 gm. child.

the index of pelvic capacity; in others, with the same smallest diameter, an easy labor may occur because in other diameters compensatory space exists which the head may utilize. However, more experience in the interpretation of pelvic type may, in the future, increase the accuracy of the obstetrical prognosis as approached by means of methods which give quantitative diagnostic information.

The second prognostic objective is concerned with fetal pelvic relationships during labor—with *how* the head engages and descends—and is important in all cases whether or not variable degrees of disproportion exist. Certain roentgen techniques from which accurate measurements of the pelvis and fetal head may be obtained from single anteroposterior and lateral films are not entirely satisfactory for the study of pelvic shape and fetal-pelvic relationships. For this purpose stereoscopic anteroposterior films, in addition to a lateral and a subpubic arch view, have been found more satisfactory. A suitable technique for making the stereoscopic films which includes a practical modification of a stereoscopic method of measurement, the so-called "phantom image" method, has been developed. By means of the precision stereoscope, diameters of the pelvis and fetal head may be measured accurately enough for practical purposes, and the pelvic shape and fetal-pelvic relationships can be studied at the same time.

To interpret the roentgenograms, the roentgenologist must acquaint himself with the problems which concern the obstetrician; namely, the size and shape of the maternal pelvis, the position and axis of the fetal head, and the existing degree of flexion, extension, or moulding. These are the factors, along with the uterine and pelvic soft parts, which control the mechanism of labor. It is difficult to describe rules to follow in the interpretation of the roentgenograms from the standpoint of *how* the head descends. However, an attempt has been made to show how a knowledge of pelvic shape and fetal-pelvic relationships may be applied to advantage in the management of labor and in the treatment of pelvic arrest.

## CONCLUSIONS

The following conclusions seem justifiable:

(1) The study of stereoroentgenograms, augmented by a lateral view and an anteroposterior view of the subpubic arch, makes possible a complete description of the shape of the pelvic cavity from inlet to outlet and leads to a classification upon the basis of morphology.

(2) The size of the pelvic diameters as determined by measurement of the phantom image in the precision stereoscope and an approximate estimate of the degree of disproportion may be gained by using the image of the fetal head as the yardstick of measurement. Any other method of roentgen pelvimetry may be used, including the comparison of head volume to pelvic size.

(3) The recognition of ample pelvic capacity and absence of disproportion gives negative evidence of value to the obstetrician, but such evidence does not preclude the possibility of soft-part dystocia.

(4) With increasing experience, the probable mechanism of labor for the pelvic type may be suggested.

(5) A knowledge of the size and shape of the pelvis and the fetal-pelvic relationships aids in the management of labor by indicating the regions where the most available space exists. In certain instances this compensatory space may be made available to the fetal head by manual or instrumental methods.

(6) In the event of arrest of the fetal head, a knowledge of pelvic shape and the existing fetal-pelvic relationship aids in showing how the best operative procedure may be employed.

(7) Positive prognostic statements as to the outcome of labor should be avoided except in rare instances, because too many immeasurable factors, which cannot be visualized by the roentgen ray, are involved.

(8) A roentgenological examination is

useful in the teaching of the mechanism of labor to the resident and intern staff of obstetrical clinics. In the discussion of difficult individual deliveries a knowledge of the pelvic type as revealed by a roentgenologic examination is necessary in order to appreciate fully the cause of the difficulty encountered.

(9) The obstetrician must acquaint himself with the visual appearance of the common obstetrical difficulties with which he is familiar. The roentgenologist and obstetrician must cooperate in an effort to correlate the roentgenologic and clinical data in each case to obtain more practical information from the roentgenograms.

The authors are deeply indebted to Dr. Ross Golden and staff of the Department of Roentgenology of Presbyterian Hospital and to Dr. Benjamin P. Watson and staff of the Sloane Hospital for Women. Their interest and cooperation in all aspects of this subject has made this investigation possible.

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# MEDIASTINAL GLANDULAR TUBERCULOSIS IN THE ADULT RESEMBLING HODGKIN'S DISEASE

## RECOVERY OF A CASE*

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THIS subject is not new. It has been discussed previously under various titles, such as: "Intrathoracic tuberculous lymphoma" (Wessler[7]); "Giant form of tuberculosis of the tracheobronchial glands in an adult" (Battigelli[1]); "Tuberculosis of the anterior mediastinal lymph nodes" (Buckley[2]), and it has also been mentioned under "Intrathoracic Hodgkin's disease" (Wessler and Greene[8]), "Tuberculous mediastinitis" (Kornblum and Cooper,[5] Felix[3]), and "Tuberculous mediastinitis" by Golden.[4] Mulky[6] has recently called attention to the difficulties of differentiating Hodgkin's disease from tuberculosis. Wessler[7] says:

"The tuberculous nature of certain forms of extensive lymphatic disease was recognized by Delafield, who in 1887 reported a universal lymphadenopathy and by Askanazy, who described a distinctive form of lymph-node tuberculosis. Clinically, these cases have occasionally been confused with pseudoleukaemia and Hodgkin's disease, which they may so closely resemble that only microscopic examination of a lymph node will reveal their true nature. On the other hand, there are cases of this pseudoleukaemic form of tuberculosis in which only bacterial staining or animal inoculation will prove them tuberculous." . . . "Baumgarten in particular sees in the pseudoleukaemic form of tuberculosis a significant relationship to Hodgkin's disease, of which he regards it as a transitional form. This view is supported by the experiments of Weingarten and Lichtenstein, who produced the microscopic appearance of Hodgkin's disease by the injection of tubercle bacilli or tuberculous lymph nodes into guinea pigs. The recent work of Fraenkel and Much has again stimulated interest in this problem. These investigators have succeeded, by the injection of lymph-node material from cases of Hodgkin's disease in which Much granules were found, in producing typical tuberculosis in animals, and they accordingly regard Hodgkin's disease as a variety of tuberculosis of the lymph nodes."

None of these discussions, however, which are more or less in the abstract, impress one so much as the difficulties involved when a colleague is suffering from this condition.

The patient was a young physician, aged thirty, who had just spent five years after graduation in one of the leading hospitals of this country and then decided to take a year of post-graduate work in Vienna. Up to this time, he had been in excellent health. While traveling on a train in Switzerland in October, 1935, on his way to Vienna, he developed a severe respiratory infection. He continued to Vienna. He then stayed in bed a week, recovering almost entirely. In December, he noticed tiredness, lassitude, some loss of weight, increasing cough, slight expectoration of mucus, but never had any hemoptysis. The cough thereafter did not entirely subside, and he never felt entirely well after that. By the end of December, he had lost 11 pounds, was increasingly tired, short of breath and had considerable cough. He suspected tuberculosis and had a chest film made in Vienna. The diagnosis from this film was tuberculosis of the hilum and mediastinal lymph nodes, and a slight tuberculosis of the left lung, subapical. The clinical opinion however differed. Three leading internists in Vienna were consulted at intervals. They first decided there was no tuberculosis, but that this was unresolved influenzal bronchial pneumonia and influenzal lymph nodes. The patient spent two weeks in the hospital on a high caloric diet. He had diathermy to the lymph nodes in the chest, ultraviolet light, etc. This gave no benefit. In the middle of January, 1936, the patient suspected Hodgkin's disease. This was refuted by the first internist, but a second roentgenolo-

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gist who examined him thought it was Hodgkin's disease. He then visited another clinic where he was told that he did not have Hodgkin's disease, but probably had "Pfeiffer's glands." Roentgen therapy was prescribed. He had 2,450 r between January 24 and February 3. It was intended to use a total of 4,000 r through each field but at this stage he was advised to return home to America. The result of the roentgen therapy was radiation sickness and additional loss of weight but no improvement. Then enlarged cervical and supraclavicular lymph nodes appeared. A third internist was consulted at the end of January, 1936. The diagnosis then was tuberculous lymph nodes, possibly primary in the nodes. No appreciable reduction in the size of the mediastinal lymph nodes could be observed before leaving Vienna.

He consulted me on March 3, 1936, just one month after leaving Vienna. He was referred to me by Dr. Charles Rein and Dr. Joseph Vandenberg of New York City. By comparing the films made on December 31, 1935, and those made by me on March 3, 1936, one could see very little difference. It seemed that the lesions, especially in the left mediastinum and hilum, had increased about 25 per cent in size. I thought even the right had increased about 25 per cent. A roentgenogram made by me at a distance of 100 inches showed a rather wide upper mediastinal shadow, measuring 7 inches laterally, with uniform lateral borders, and about the roots of the lung and about the hilum on each side, there was shown a conglomeration of mass of glands, making a total mass in the left hilum of the lung 8 cm. in length and approximately 4 cm. in width; on the right side, measuring 8 cm. in length and approximately 3.5 cm. laterally. At the inner border of the left first interspace, there was a circular mass or shadow approximately 2 cm. in diameter, and two similar circular shadows in the left second interspace. In addition to this, there was a group of very small lymph nodes extending upward along the right bronchial tree. These shadows suggested peribronchial infiltration rather than parenchymal infiltration. There was in addition in this film a number of fine shadows 2 or 3 mm. in diameter scattered through the lung fields on both sides, which I believed were probably also peribronchial. Any of this appearance could be duplicated by Hodgkin's disease (Fig. 1).

In the lateral view, in the film made on Feb-

Fig. 1. Roentgenogram made on March 3, 1936, shows the parasternal mediastinal lymphomata and also the localized lymphomata in the region of the inner portion of the first interspace and outer portion of the second interspace on the left side. Notice the numerous fine miliary-like deposits elsewhere in the lung area.

ruary 3, 1936, in Vienna (the complete records of both the examinations and the treatment had been forwarded to me), there are shown sharply defined tumor masses occupying the entire upper three-fourths of the mediastinum. In its upper portion, this mass extends from the spinal column to the sternum. In the lower two-thirds of this glandular mass, there is an undulating border extending downward and at the lower portion it involves about one-fourth of the distance from the anterior borders of the spinal column to the sternum (Fig. 2).

These lesions taken together with the palpable lymph nodes and without any history would certainly lead any roentgenologist to think first and almost finally of Hodgkin's disease. The distribution of the glandular enlargement seemed to be that of Hodgkin's disease, but I had never seen a case of Hodgkin's disease which had the amount of treatment which was given to this patient without producing some striking improvement. We therefore decided on the first day he consulted me to remove one of the lymph nodes for microscopical diagnosis. A lymph node in the left supraclavicular region which had not been irradiated was removed by Dr. William Bates of Philadelphia and also a lymph node from the right supraclavicular region which had been irradiated was removed. The microscopical examination was made by Dr. Eugene Case, Professor of Pathol-

Fig. 2. Roentgenogram made on February 3, 1936, shows rather sharply defined tumor masses involving the upper two-thirds of the mediastinum. Much more tumor tissue shown in the lateral view than in the anteroposterior view.

ogy of the Graduate School of Medicine of the University of Pennsylvania. The following is Dr. Case's report: "Grossly these lymph nodes are enlarged and upon cut section, more or less translucent. Microscopically the lymph node tissue has been replaced by small rounded lesions made up of epithelioid cells. In the centers of some of these rounded areas there are attempts at the formation of giant cells. There is an increase in the fibrous tissue. So far as I could determine there is no difference in the appearance in the one irradiated and the one not irradiated. The sections were searched for tubercle bacilli but none were found. Diagnosis: Tuberculous lymphadenitis." Dr. James Ewing saw the slide and said that Hodgkin's disease could be absolutely ruled out, and that this was a hyperplastic (primary glandular) tuberculosis.

We therefore concluded that these lymphomata in the mediastinum were tuberculous and since there had been no response to irradiation previously, it did not seem advisable to keep him in the city for further irradiation. It seemed advisable that he be placed under treatment for tuberculosis with perhaps the addition of small doses of roentgen therapy. This opinion as to diagnosis and treatment was confirmed by Dr. Lloyd Craver of the Memorial Hospital, New York. As a result, this patient went to Tucson, Arizona, where he stayed for one year. During this time, serial roentgenograms were made. *No further roentgen therapy was used.* A film made on June 22, 1936 (Fig. 3), after his clinical symptoms had disappeared and he was symptomatically improved, showed that at least three-fourths of the evidence of the disease in the original film made by me had disappeared. The roentgenogram made on August 12, 1936, showed no appreciable change as compared with the one made June 22, 1936. At the middle of this period, a roentgenologist in Tucson still made a diagnosis of Hodgkin's disease and sent a set of films to one of the leading clinics in this country where the diagnosis of Hodgkin's disease was again confirmed. On October 15, 1937 (Fig. 4), I re-examined him. At this time, his lung fields were entirely clear, and there was no more abnormal shadow in the mediastinal area and the hilum of each lung than one commonly finds in any chest with infection secondary to accessory sinus disease. The lateral film also showed complete disappearance of the tumor in the mediastinum.

He gradually recovered, and on March 21,

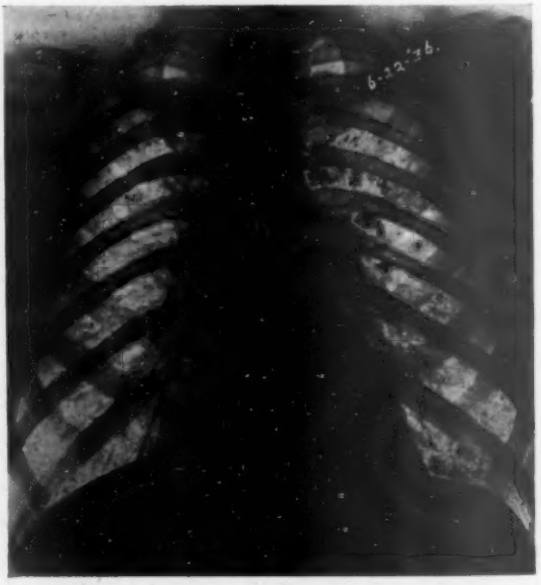

Fig. 3. This roentgenogram made on June 22, 1936, shows disappearance of about three-fourths of the glandular enlargement. The lymphomatous conditions in the chest and second interspace on the left side have disappeared and the lung fields are now clear.

1938, when I re-examined him, all evidence of disease had disappeared except a slight increase over normal in the hilar shadows which is probably due to a fibrous tissue process. Re-examination made July 6, 1938, showed no disease. This case illustrates better than any line of argument the great difficulties that must necessarily be involved in differential diagnosis, for all of the differing opinions expressed in his case came from men of wide experience. They were all internists and roentgenologists who had a very extensive clinical experience and whose opinions must be respected by everyone. All names of the physicians have not been mentioned for it would add nothing.

The importance of making a diagnosis is also well illustrated in this case. This young man's life and career depended upon accurate diagnosis and correct treatment. This is probably true in every case but so often in our great mass of work, we are apt to look upon these problems more or less in the abstract, instead of concrete living problems. So far as one may judge from the literature, recovery must be very rare. This patient recovered.

In this case, ten examinations of the sputum

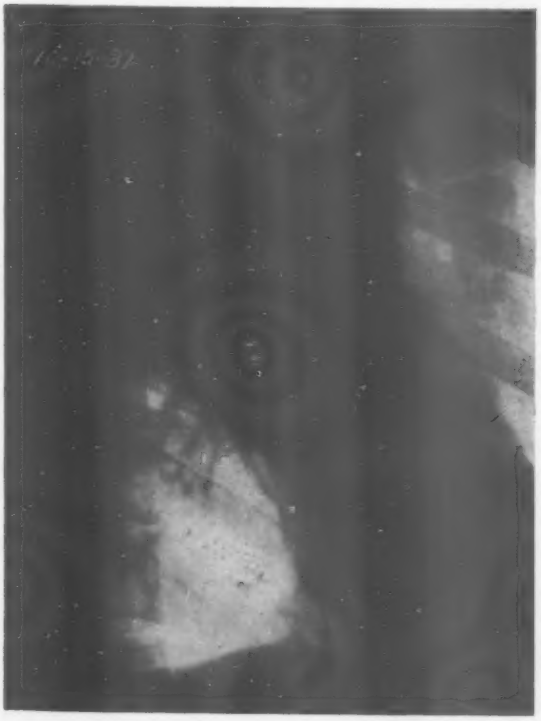

Fig. 4. An oblique view made on October 15, 1937, showing the mediastinum entirely clear of glandular tissue.

Fig. 5. This roentgenogram made on March 21, 1938, shows both the lung fields and the mediastinum clear.

for tubercle bacilli between January 2, 1936, and July, 1936, were negative. The blood showed mild anemia at first; hemoglobin, 80–85 per cent; red blood cells, 4,000,000; white blood cells, 7,000; differential: mild elevation of lymphocytes, otherwise normal; eosinophiles 3 per cent. By July, 1936, the anemia had disappeared and the blood count through 1937 was hemoglobin, 100 per cent; red blood cells, 5,500,000; white blood cells, 7,500; differential: neutrophiles, 65 per cent; lymphocytes, 28 per cent; eosinophiles, 2 per cent. Blood sedimentation rate was greatly elevated in January, 1936, 60 mm. in sixty minutes (Westergreen). Sedimentation normal since July, 1936. Tuberculin test July, 1936, 1:100,000 O.T. 3 plus. Temperature, normal or half degree elevation in January, 1936, normal thereafter.

### DIFFERENTIAL DIAGNOSIS

It has been said that the first essential in making any diagnosis is to think of the disease, and also to think of the various conditions with which the diagnosis may be confused. It is well known that glandular mediastinal tuberculosis is common in children. All of Wessler's cases of tuberculous lymphoma were between the ages of

nineteen and twenty-five, and therefore they must be classed as young adults. The age of the patient reported here was thirty. Wessler's patients, with one exception, had definite evidence of tuberculosis which manifested itself in the usual way of fever to a moderate degree, weakness, loss of weight. In addition, there was such less common evidence as toxemia, purpura hemorrhagica and rheumatic pains. The symptoms had existed from two to six months, but in one case three years. The mere fact that there are only relatively few cases of this type of tuberculosis recorded in the literature indicates that it is a rather rare disease. Leukemia, lymphosarcoma and Hodgkin's disease which cause similar enlargement of the lymph nodes are much more common.

Tuberculosis of the peribronchial lymph nodes in infants manifests itself by massive enlargement and extensive caseation. This is regarded in general as the reaction to a primary focus in the lung which appears to be brought about because of the wide lymphatic channels in the infant, and because of relative sensitivity of the lymph nodes which has not been modified by some previous tuberculous infection. If the infant survives infection, the lymph nodes undergo gradual induration and calcification and become smaller. For some reason, after this reaction in the lymph nodes has taken place in children, subsequent exposure to infection in later childhood or adult life rarely causes much enlargement. Therefore, the bronchial lymph nodes which are so commonly found in the adult are small, indurated and anthracotic. Ordinarily the small lymph node tuberculosis as seen about the hilum in the roentgenogram in the adult produces no symptoms and has no clinical importance.

Through the courtesy of my former associate, Dr. B. P. Widmann, and his assistant Dr. Herman Ostrum, I had the privilege of examining some of the films made at the Philadelphia General Hospital which also showed this glandular tuberculosis in adults. In those cases, however, practically all showed a definite pulmonary tuberculosis and in nearly all other cases of glandular tuberculosis that I have seen in the adult the lymphomas are less massive, and they were less sharply defined. In other words, there was an invasive appearance extending into the lung fields, more like those occurring in tuberculous mediastinitis. The problem of differentiation, therefore, between Hodgkin's disease and tuberculosis involving the mediastinum only arises when one is dealing with this rare form of massive, rather sharply defined tuberculous lymphoma and when no definite lung involvement is present. Hodgkin's disease seems to affect by preference especially the right paratracheal lymph nodes. It is true that we also find Hodgkin's disease with an invasion into the lung areas, but generally one has associated palpable lymph nodes which are more definitely Hodgkin's disease than the small lymph nodes shown in my case.

Lymphatic leukemias can of course give rise to massive tumors in the mediastinum exactly like these but the blood studies will serve to make the differentiation.

Lymphosarcoma can give an identical roentgen picture, and the lymphosarcomata may be confined to the mediastinum. One may not have palpable lymph nodes for resection and for microscopical examination. Lymphosarcoma, however, is more sensitive to irradiation than are these tuberculous lymphomata.

Hodgkin's disease is also much more radiosensitive. The differential diagnosis, therefore, may have to be made by judging the radiosensitivity of the tumor tissue.

When there are associated lymph nodes, it seems that it would be advisable very early to remove a lymph node and examine it microscopically so as to make the definite differential diagnosis. It is only in those cases in which there are no palpable lymph nodes to be removed for microscopical examination that the diagnosis seems especially difficult. At the beginning, in my case under discussion, there was no lymph node enlargement externally. If

there had been no enlarged lymph nodes when I saw him I would have considered first of all Hodgkin's disease, as the probable diagnosis as was done in Vienna. *It was the lack of response to irradiation given in Vienna which made me think that we were not dealing with Hodgkin's disease.*

The importance of a discussion of this subject is shown by the fact that even after the microscopical examination had been made, and even after the disease had responded to treatment and rest, several capable roentgenologists still made a diagnosis of Hodgkin's disease. The cases that have associated pulmonary tuberculosis with definite pulmonary involvement are also more easily diagnosed. In the case under discussion, the roentgen appearance and the clinical evidence had indicated an involvement of the parenchyma of the lungs but this appearance I believe was probably due to the peribronchial glandular infiltration and enlargement, and not an actual parenchymal involvement.

## SUMMARY

1. A case of mediastinal glandular tuberculosis of the primary childhood type occurring in a man, aged thirty, has been reported, in which the diagnosis of Hodgkin's disease was made repeatedly by various competent roentgenologists in different parts of the world and by competent internists. This illustrates the difficulty and importance of considering tuberculosis in every case of mediastinal Hodgkin's disease or lymphosarcoma.

2. When there is associated enlargement externally of the lymphatic glands, it would seem advisable to avoid delay by removal of a gland early in the diagnostic procedures. This may be done more safely after preliminary irradiation, especially when lymphosarcoma is suggested.

3. Differentiation may have to depend upon the degree of radiosensitivity of the mediastinal tumor. The radiosensitivity would probably range progressively from Hodgkin's disease, lymphatic leukemia, lymphosarcoma to tuberculous lymphoma.

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## DISCUSSION

Dr. Lloyd F. Craver, New York City. I think it is a very timely subject that Dr. Pfahler has brought to our attention, as it is my impression that more and more of these cases of hilar lymphadenopathy are coming to us at Memorial Hospital. Unfortunately, in the great majority of these cases, we do not have the advantage of a biopsy of a superficial lymph node as was possible in this case. If a biopsy of a superficial lymph node gives a diagnosis of tuberculosis, usually of the hyperplastic type, one is probably 99 per cent sure that the hilar lymphadenopathy is also tuberculous. Yet I feel that there is perhaps the 1 per cent or so element of doubt about it.

We know perfectly well that in many cases of lymphadenopathy in which a diagnosis of tuberculosis is given by one biopsy, it may be possible that another part of the lymphadenopathy may be Hodgkin's disease, and vice versa. Yet that element of doubt is probably a very small one and of little importance; when there is a clean-cut diagnosis of tuberculosis from the biopsy, one is pretty nearly 100 per cent sure.

In the cases in which we cannot have a biopsy, what are we going to do to establish the diagnosis? The thing that we like to do in many of these cases is to perform a tuberculin

test. We know that in many cases of Hodgkin's disease, the tuberculin test may be negative. If we get a negative tuberculin test in such a hilar and tracheobronchial lymphadenopathy as this, we tend to suspect that the diagnosis may be Hodgkin's disease. There again, though, there may possibly be some element of doubt.

What we do in such a case is to try very small doses of roentgen radiation, beginning usually with about 50 r of high voltage roentgen rays, through a rectangular portal designed to include the two hilar masses, because those are the ones which we can follow best from the roentgen film, and usually ignoring the upper anterior mediastinum. Then we wait ten days or two weeks or longer to see whether any reaction occurs, such as one might expect if one were treating a tuberculous lymphadenopathy. If no reaction occurs after that interval, then we may proceed with another dose of 50 or 75 r. Frequently, we give that treatment at 70 or 100 cm. so as to get a better depth dose.

Following such cases along that way, feeling the way along, one may be able then, after two, three or four months, to get a little indication of what changes are occurring. My impression is that in the tuberculous lymphadenopathy, a very small degree of regression may occur.

That happened in a case which preceded this case which Dr. Pfahler reported, likewise a physician, but in whom we did not have any biopsy. After an observation of three months in this way and seeing a very slight regression, we sent him to Arizona. In one year he was perfectly well and he has remained well ever since. However, I think that the majority of cases which we have of this type, as far as I can see at present, react more like Hodgkin's disease.

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# INTERSTITIAL CALCINOSIS

## REPORT OF A CASE AND REVIEW OF THE LITERATURE

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THE term "calcinosis" is used to imply a pathological condition of unknown etiology in which there is an abnormal deposition of calcium salts in the soft tissues of the body. In 1878 Weber[28] described the condition in association with scleroderma. Later Krause and Trappe[19] suggested for the generalized form of the disease the use of the term calcinosis interstitialis universalis. Although many reports of patients suffering with this disease have appeared in the literature, chemical and histopathological studies are few and limited in scope. The purpose of this report is to present detailed studies of a patient with diffuse interstitial calcinosis together with a review of the literature.

### CASE REPORT

*A white male, aged sixty-two, had for four years shown gradually increasing evidence of benign prostatic hypertrophy and hypertension. Multiple nodules had appeared over the small joints after local trauma. Laboratory findings disclosed marked azotemia, moderate secondary anemia but normal concentration of calcium in the blood serum. The nodules were radiopaque and consisted of gray cheesy material, containing calcium, phosphorus and magnesium in approximately the usual proportion for calcified structures in the body. Autopsy revealed bilateral pyelonephritis, benign prostatic hypertrophy, and normal parathyroid tissue and bone marrow.*

The patient, E. H. (No. 24693), a white, male farmer, aged sixty-two, was admitted to the Hospital of the University of Pennsylvania for a prostatic resection, November 20, 1936. He had been well until four years previously, at which time he had developed marked frequency of urination and was told by his physician that his blood pressure was elevated. Two years before admission his urinary symptoms had increased so that difficulty in voiding had necessitated catheterization on several occasions. In addition, he had noted cramp-like pains in both great toes and calves. In August, 1936, the patient fell during an attack of vertigo and injured slightly the left lateral thoracic wall and the right arm just below the elbow. Two weeks later the traumatized areas became sore to the touch, and lumps appeared in these regions. These were not tender but enlarged progressively to the size of an English walnut. They were always quite firm. There was no tendency to suppuration. In September, 1936, the patient himself milked his cows for the first time in more than a year. During the next few days his fingers became stiff and painful, and after two weeks small non-painful nodules appeared on the dorsum of the phalangeal joints of the hands. He experienced pain in the shoulders, hips, elbows and interscapular space. A physician opened one of the pea-sized nodules and expressed a white chalky material. Healing was slow. Three weeks before admission progressive weakness forced the patient to remain in bed. His weight had decreased from 176 pounds in 1934 to 124 pounds at the time of admission.

The following additional symptoms were elicited: Progressive weakness for many years; fatigue during the past year; dyspnea on exertion for fifteen years, recently increasing; frequency, urgency, pain and burning on urination and nocturia. During the year prior to admission, the patient's diet had been greatly curtailed voluntarily and had consisted of whole wheat cakes, molasses and fruit juices; he had eaten no meat or vegetables during this period.

His past medical history included an attack of "rheumatism" in both knees and feet in 1918, necessitating three months rest in bed. The patient had never used alcohol or tobacco. The family history was unimportant.

On physical examination the significant findings included: Normal temperature, pulse, and respiration; blood pressure of 160 mm. Hg systolic and 90, diastolic; evidence of marked loss of weight; pallor; small, buried tonsils; upper, compensated edentia; slight cardiac enlarge-

FIG. 1. Calcifications about the shoulder. These may be confused with deposits in the supraspinatus tendon.

ment, with an apical systolic murmur; moderate enlargement of the liver; a palpable right kidney; distention of the urinary bladder; a greatly enlarged, benign prostate; absent patellar and Achilles reflexes; and numerous superficial nodules. These latter, varying in size from a pea to a walnut, were found over the right olecranon process, at the bases of the distal phalanges of the fingers on the dorsal aspect, attached to the tenth rib in the left posterior axillary line, and on the dorsa of several of the toes. The nodules were firm, resilient or rubbery in consistency, not tender, and somewhat movable. On palpation it was thought that they contained fluid under pressure. The lesions were conical in shape.

Laboratory examinations showed: 2.1 million erythrocytes per c.mm.; 10,800 leukocytes per c.mm.; 6.2 gm. hemoglobin per 100 ml. of blood; a normal differential picture, and negative blood Wassermann reaction. The urine contained many erythrocytes, clumps of leukocytes, and a cloud of albumin. The specific gravity of the urine ranged from 1.010 to 1.015. The concentrations of various components of the blood and blood serum were as follows: Blood urea nitrogen, 125 mg. per 100 ml.; serum proteins, 5.2 gm. per 100 ml.; serum calcium, 10.3 mg. per 100 ml.; serum chloride, 100 m Eq/L; serum total carbon dioxide, 28 volumes per cent; serum phosphorus (inorganic), 6.9 mg. per 100 ml.; serum magnesium, 2.9 m Eq /L; sodium, 120 m Eq/L; serum cholesterol, 225 mg. per 100 ml.; blood uric acid, 6.4 mg. per 100 ml.; and blood sugar, 94 mg. per 100 ml. The direct van den Bergh reaction for bilirubin in the serum was delayed; the indirect read 0.1 mg. per 100 ml. The excretion of phenolsulphonephthalein totaled only a trace in two hours.

An electrocardiogram showed left axis deviation, slurring of the QRS complexes, and diphasic T waves in lead I.

Roentgen examination included the entire skeleton, a report of which follows.

*Skull:* There was calcification of the choroid plexus in each lateral ventricle and in the region of the vessels of the circle of Willis.

*Neck:* There were small, ring-like densities on each side of the cervical spine.

*Thorax:* Adjacent to the edge of the upper ribs on both sides were many small, round, dense shadows. Beneath the outer edge of each clavicle were deposits of opaque material somewhat linear in arrangement.

*Chest:* In the left lung field was a densely calcified deposit, which resembled a calcified lesion resulting from previous tuberculous infection.

*Shoulders:* About both shoulder joints one could identify many rounded, soft calcifica-

FIG. 2. Note the conglomerate shadow along the ulna. A few indefinite calcium deposits are adjacent to the tip of the olecranon process.

tions. Some of these were in the customary position of calcified deposits in the supraspinatus tendon (see Fig. 1).

The deposits of calcium appeared as nongranular, soft, round shadows which were predominantly adjacent to joints. There were no changes in the joint spaces. The bones of the skeleton showed normal density. No such changes in the digital tufts as have been described in scleroderma were seen.

Fig. 3. Multiple amorphous calcium deposits are present. Most of these are adjacent to the joints.

*Elbows:* Many minute calcified deposits were present about these joints. Just distal to the base of the right olecranon process was a collection of such deposits (Fig. 2).

*Hands and Wrists:* Many small and some large deposits of the opaque material were seen particularly along the metacarpals and phalanges of each index finger. The calcifications were for the most part adjacent to the joints (Fig. 3).

*Abdomen:* No calcification was seen.

*Pelvis:* Many calcified deposits, which varied in size from a millimeter to an inch in diameter, were distributed along the rami of the ischii and above each greater trochanter (Fig. 4). In the large vessels of the pelvis and thighs were irregular areas of calcification.

*Knees:* A few deposits, about the size of the head of a pin, were scattered in the region of both knee joints and particularly along the edges of the proximal end of each tibia.

*Feet and Ankles:* Many dense deposits were present. The largest of these were along the shaft of the fifth metatarsal (Fig. 5).

A tentative diagnosis of calcinosis was made. In order to obtain material for chemical and

Fig. 4. Calcium deposits are present near the right hip. They are homogeneous in character and soft in appearance.

microscopic examination, a biopsy was performed upon one of the nodules over the olecranon process. A multinodular mass about the size of a large walnut was exposed. It was found fixed to the underlying structures. In one spot the skin was adherent to the mass. The nodules extended to the heavy aponeurosis overlying the muscles on the extensor aspect of the arm. The tumor did not reach the bone except in one very small area where the periosteum had been penetrated and the cortex eroded, leaving a hole 1 mm. deep and 4 mm. wide. The mass excised consisted of one large nodule surrounded by several smaller ones. These nodules contained a white, toothpaste-like material. A few of the nodules had a cartilaginous consistency.

FIG. 5. Calcium deposits in the soft tissues of the feet. The blood vessels of the feet also show calcium deposits.

On microscopic examination (Figs. 6 and 7) by Dr. Herbert Fox, it was found that the specimen was composed of fibrous connective tissue, containing in places foreign body giant cells which were surrounded by a more cellular stroma. The cells were predominantly inflammatory. The larger areas were broken down and cystic in their centers, the largest being about 0.5 cm. in diameter. Most of the contents of the cysts had fallen out in the preparation of the slides. What remained was globular, irregular, non-crystalline, occasionally laminated droplets of inorganic material. In frozen sections this material stained purple with hematoxylin and eosin and more deeply with Cameron's alizarin stain. Stained with von Kossa's silver nitrate, it was brownish-black to jet black. Sudan IV (scharlach R) demonstrated the presence of globules resembling free fat in the densely packed connective tissue immediately surrounding the cystic areas and trailing off into the lower connective tissues. This was seen both in the frozen sections and in the formalin fixed preparations. The connective tissue about the cysts was dense but not very cellular. The presence of free fat, the foreign body reaction, the granulation tissue, and the cyst formation with the deposition of an inorganic matter presumably calcium, seemed consistent with the diagnosis of local calcinosis from inflammation with fat deposit.

Chemical examination was performed on the material obtained from several of the subcutaneous nodules. Two grams of the creamy substance were dried at 100° C. to constant weight and then ashed. The following analyses were obtained:

Solids (dried weight): 33.5 per cent of the wet material.

Ash in dried material: 72 per cent.

Calcium: 49.3 gm. per kilo or wet material.

Phosphorus: 34.2 gm. per kilo of wet material.

Magnesium: trace.

Approximately 2 grams of the tissue were ground with 35 cc. of water. The aqueous extract contained 0.014 mg. of uric acid per cc. After extraction with water, the tissue was ground with 50 cc. of a mixture of three parts of alcohol and one part of ether; this extract contained 1.7 mg. of cholesterol per ml.

The patient's condition on admission was critical. Despite the use of bladder decompression, indwelling catheter, parenteral fluids and multiple transfusions, the patient grew worse gradually and died January 10, 1937.

Autopsy revealed: Normal thyroid and parathyroid tissue; inactive rheumatic valvulitis; arteriosclerotic valvular heart disease; left ventricular hypertrophy; myocardial focal fibrosis; healed fibrous pulmonary tuberculosis, anthracosis, senile emphysema, and atelectasis of the left lower lobe; chronic passive congestion of the liver; senile atrophy of the pancreas; mild follicular hyalinization of the spleen; bilateral pyelonephritis with abscesses in the left kidney and bilateral hydronephrosis, subacute cystitis, benign prostatic hypertrophy, and chronic urethral obstruction. The nodules studied consisted of a pasty central zone containing calcium surrounded by a wide granulomatous zone of fibroblasts and giant cells with a dense fibroid capsule. Diagnoses following the autopsy were: Benign prostatic hypertrophy, pyelonephritis, azotemia, recent formation of radiopaque deposits, and terminal uremia.

FIG. 6. The cellular wall of a cyst-like area in which the white pultaceous calcium carrying material is found. The black amorphous masses scattered through the cellular zone, stained by alizarine and hematoxylin, may be accepted as calcium. Fat globules also scattered in the cellular zone and also in the fibrous tissue about it. Note especially the higher cellular construction of this zone which was of distinctly chronic granulomatous character.

FIG. 7. Chronic fibrous construction with granuloma-like nodules away from the cyst-like areas of Figure 6. Black masses took alizarine and hematoxylin and therefore probably calcium. One distinct granuloma or tubercle with giant cells containing black masses; smaller mononuclear cells all surrounded by a distinct fibrous capsule.

The association in this patient of an elevated blood uric acid and hard nodules about the joints suggested at once the possibility of gout; however, the nodules were opaque to the roentgen rays and on analysis contained calcium rather than urates. The elevation of blood uric acid was probably the result of a long standing progressive glomerulonephritis. Xanthomatosis was considered as a clinical possibility but the blood cholesterol was normal, and the cholesterol content of the excised nodules was extremely low. Because of the discharge of a creamy material from the masses, infection with mycoses was thought of, but was dismissed when cultures of the cheesy material on Sabouraud's medium and repeated smears were negative for these organisms. The finding on roentgen examination that the masses contained

large amounts of calcium led to a discussion of the conditions in which abnormal calcium deposits have been found. These include: (1) stone formation (renal, biliary, pancreatic, salivary, and bronchial); (2) calcium deposits in dead or dying tissue (dystrophic calcification of Barr); (3) vascular calcifications: phleboliths, calcified atheromata, calcified hematomata, arterial; (4) metastatic calcifications (of Virchow): in multiple myeloma, myelogenous leukemia, in association with sarcoma and carcinoma metastatic to bone, Albers-Schönberg's disease, in association with osteomyelitis, in caries of the spine, hyperparathyroidism, and chronic nephritis; (5) calcinosis (calcium deposition in the skin and subcutaneous tissues) circumscribed and universal; (6) unclassified: calcified bursae and tendons, pulmonary osteo-arthropathy, osteitis deformans (Paget's disease), true osteomas of the skin, calcified fat lobules on the inner side of the legs appearing in the aged, myositis ossificans, calcification associated with scleroderma, dermatomyositis, Raynaud's disease, and dietary causes. A complete discussion of these conditions does not fall within the scope of this paper. The reader is referred to the excellent report of Barr[2] for this information.

This patient had several of the conditions that may be conducive to a focalization of calcium deposits. The calcified nodules were seen especially at points of trauma. There was an arteriolar degeneration. Calcified changes are not infrequent at points of injury, especially when favored by vascular degeneration. The presence of cramp-like pains in the extremities supports this. The existence of fat and the very evident chronic inflammatory reaction may have been added to the effective trauma and the calcium imbalance of the chronic nephritis. We do not feel that calcinosis is a disease entity, but that it is merely a pathological condition dependent upon other fundamental causes. A more proper term than calcinosis may be one such as extra skeletal calcium dystrophy.

The roentgen differential diagnosis requires consideration of calcified bursae, calcification in the tendons, myositis ossificans progressiva, hyperparathyroidism, calcareous gout, calcified vessels or thrombi, Raynaud's disease, and calcified parasitic infestation. In this patient, the soft appearance of the lesions and their proximity to the joint spaces suggested the possibility of calcified bursae or tendons. However, such calcification is not usually so widespread and is most frequently seen about the shoulder girdle and hip joint. Myositis ossificans progressiva is characterized by irregular spikes or bands of bone, particularly prominent in the region of the flat bones; one may also find bony defects in the hands and feet due to defective ossification. Hyperparathyroidism can be excluded because cystic lesions and demineralization of bone are not a part of the roentgen picture of calcinosis; in our case there were no urinary deposits and the distribution of the calcification was unusual for parathyroid disease as we have seen it. The absence of changes in bones or joints is not compatible with generalized gout or scleroderma. Calcification as a result of infestation with parasites is uncommon in this geographical location; the variable size and shape of the lesions presented by our patient indicated that this possibility was quite unlikely.

## DISCUSSION

The term calcinosis as now used refers to deposition of calcium salts in the skin and subcutaneous tissues. Synonyms for this term include hypodermoliths, hypodermolithiasis, petrification of the skin, dermal and subdermal concretions, gout stones, lime gout, calcareous subcutaneous concrements, granular deposition of lime, chalk gout, calcinosis interstitialis, Profichet's syndrome, et cetera. Reviews of the literature have been presented by Steinitz,[25] Weissenbach *et al.*,[29] Rothstein and Welt,[22] Epstein,[9] Brooks,[5] and Scholz.[23]

The etiology of calcinosis remains unknown. The condition has been noted in

combination with other diseases such as scleroderma or sclerodactylia, Raynaud's disease, chilblains, acrocyanosis, and muscular fibrosis. In a single instance two siblings showed the disorder.[5] Cold, trauma, inadequate nutritional conditions, renal disease, hypervitaminosis D,[32] endocrine abnormalities and degeneration of fat lobules have been suspected as having etiological importance. Barr[2] was inclined to view the disease not as a generalized disturbance in calcium metabolism but as an expression of locally damaged tissue, especially when it occurs in the nutritional defects of Raynaud's disease or scleroderma.

It is commonly accepted that calcification does not occur in normal tissues, except bone and cartilage. Any dead or degenerating tissue, if not absorbed, may undergo mineralization, usually with calcium salts. Kleinmann[16] found necrotic areas alkaline and associated their tendency to become calcified with the observation[6] that alkalinity favors precipitation of calcium salts *in vitro*. Fatty degeneration has frequently preceded calcification of the soft tissues; hence Klotz[17] suggested that the formation of calcium soaps, subsequently transformed into calcium phosphate and calcium carbonate, constitutes the mechanism of calcification.

Virchow[27] first described calcification of the metastatic type, based on 5 cases of destructive disease of the skeleton, associated with nephritis; he stressed the importance of a renal lesion in the pathology of this condition.[20] The selection commonly of the stomach, kidneys, and lungs as the site of such calcium deposition, in the absence of degeneration or inflammation in these tissues led Askanazy[1] and later Hofmeister[12] to suggest that the relative alkalinity of these three organs, which excrete or secrete acid substances, might promote the deposition of calcium. Magnus and Scott[20] have pointed out that this theory is not applicable to the cases recorded in the literature in which the stomach, kidneys and lungs have escaped, but the arteries and skin have been severely affected. They suggested that possibly chronic disturbance of renal function may deplete the tissues of calcium to a degree sufficient to stimulate the parathyroid glands to overactivity; then if a long enough period has elapsed, these latter may undergo hyperplasia to a degree sufficient to overcompensate.[21]

It has been shown that calcium may be deposited in any connective tissue if the blood supply has been decreased.

*Pathology*. Complete pathological examinations have been reported in very few patients suffering with calcinosis. The frequent association of calcinosis with scleroderma and with Raynaud's disease has been mentioned. A significant number of the patients with this combination exhibited chronic nephritis. A few observers have demonstrated that the calcium deposits consisted of calcium carbonate and calcium phosphate,[3,33] the ratio of calcium to phosphorus closely simulating that found in normal bone.[18] Traces of magnesium have also been found.[13] According to Wells,[30] the chemical composition of the concretions has been approximately the same as that of calcified structures elsewhere in the body: calcium phosphate 86 per cent, calcium carbonate 13 per cent, and magnesium phosphate 1 per cent. Traces of cholesterol have been present rarely. Scholz[23] noted a marked hypertrophy of the interstitial connective tissue which in certain areas had undergone degeneration, in which latter areas calcium deposits were found. No pathological changes have been found in the bones. The muscles have contained no calcium deposits even when in certain areas they showed degeneration. The hard subcutaneous nodules have been calcium deposits within hypertrophied fibrous tissue. No differences in the lesions have been observed between those of calcinosis circumscripta and of calcinosis universalis.

*Clinical Picture*. The multiple calcium deposits of this disease occur in the skin, subcutaneous tissues and deep-seated interstitial connective tissues. When the disease has been noticed first in adult life, about 30 to 50 per cent of the cases have

had either a long standing scleroderma, peripheral vascular disease, or Raynaud's disease. The earliest symptom is often soreness or tenderness of localized areas of skin. Examination then reveals single or multiple, discrete, firm or quite hard nodules, movable at first, but later when large becoming fixed. The nodules may cause no discomfort. The skin over them may break down and a grayish chalky material may exude. The lesions characteristically develop in areas in which trauma may occur: the fingers, elbows, knees, and buttocks. They are rarely seen on the trunk, face, or scalp.

The circumscribed form has occurred most frequently in adults, especially in females. It most commonly involves the fingers and has been called by some writers calcium gout. Breakdown of the lesions with subsequent scar formation may limit the motion of the joints; usually there is no change in general health.

The generalized form, calcinosis universalis, is most frequently seen in children and has a poor prognosis.

The presence of hard, small, subcutaneous nodules is the outstanding clinical feature of the disease. The nodules either remain rather small or enlarge very slowly. In the later stages of the diffuse form muscular atrophy, contractures and ankylosis develop. This form usually develops insidiously and its course is slow, with remissions and intermissions. The onset of the localized form may at times be acute. Complete recovery has not been reported in either form.

*Laboratory Findings.* No variations have been found from normal figures of the complete blood count, urinalysis, blood sugar, uric acid, serum proteins, calcium, phosphorus, and cholesterol. Blood Wassermann reaction is usually negative. Stool examinations show nothing unusual. Occasionally the blood phosphatase has been found[4] to be elevated.

*Roentgenologic Findings.* The calcified areas vary in size and may be quite large, especially in juxtaposition to the large joints. They may be at different depths either in the subcutaneous or in the deepest interstitial tissues. They are not connected with bone. The bones show no demineralization; arthritic changes are usually absent. In the diffuse form of the disease the calcium deposits are most commonly in the extremities.

*Prognosis.* When the disease occurs in adult life, the calcinosis will probably persist but will very rarely impair the general health or shorten life. In mild forms of the disease the lesions may remain at one stage of development for many years. Occasionally a superficial nodule may be reabsorbed. These lesions do not undergo malignant degeneration. The prognosis in the generalized form of the disease is poor, although marked improvement has been reported in some cases.

*Treatment.* Some improvement has been obtained with various forms of therapy, including the administration of a ketogenic diet,[15] disodium phosphate,[7] ammonium chloride,[3,24] and following intercurrent infection.[14] The ingestion of ammonium chloride increased the output of calcium in the urine in one case.[3] Absorption of ingested calcium and phosphorus has been greatly reduced[5] by increasing the alkalinity of the intestinal tract, with at times decalcification of the skin deposits by demands from the skeleton. Among the ineffectual therapeutic agents may be included the administration of desiccated thyroid; anterior pituitary, parathyroid, and other tissue extracts; roentgen therapy to various of the endocrine glands; a low purine diet; and diathermy locally applied. Recent investigators favor the use of a diet with low calcium and low vitamin D content. Salts which after absorption have an acidifying effect may be given to aid in the elimination of the calcium deposits. Abscesses should be drained, and if any of the calcified nodules cause pain or limitation of function, they may be removed surgically.

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# THE ROENTGEN DIAGNOSIS OF IDIOPATHIC STEATORRHEA AND ALLIED CONDITIONS

## PRACTICAL VALUE OF THE "MOULAGE SIGN"*

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A CONSTANTLY increasing number of cases of "idiopathic steatorrhea" is being recognized in the countries of the temperate zone. This interesting clinical syndrome is closely related to tropical sprue and includes, in addition to the "non-tropical sprue" of adults, the disease of childhood variously known as Gee's disease, celiac disease, Herter's disease, intestinal infantilism, and "celiakie"; idiopathic or intestinal tetany; and the steatorrhea associated with certain organic diseases such as lymphosarcoma of the intestine, lymphosarcoma of the mesenteric lymph glands, and gastrocolic fistula. Common to all these conditions is a failure of small intestinal absorption of fat, carbohydrate, and calcium, and sometimes phosphorus as well. In some instances antianemic factors and important vitamins are also apparently unabsorbed. The disease is strictly a failure of absorption, since there is no difficulty in splitting either the fats to fatty acids and soaps, or the carbohydrates to the simple sugars, because the corresponding ferments are present and active. Quantitative studies show that in the acute phases of the disease there is little or no rise in the blood fat (Fanconi,[9] Barker and Rhoads[1]) or blood sugar (Thaysen,[30] Fairley[7]) after the ingestion of these foodstuffs, and that the dried feces contain 30 to 60 per cent of fat as against a normal average of 7 to 28 per cent (Peters and Van Slyke[23]) or 20 to 30 per cent (Pratt[26]) on a mixed diet. The result of this loss of two of the three chief classes of foodstuffs is usually a persistent diarrhea, characterized by the passage of voluminous, foul, greasy, or more commonly, frothy and soapy stools, and oftentimes so great a progressive wasting of the body tissues as is seldom seen in ambulant patients. The calcium loss, resulting from combination of this mineral with the unabsorbed fat in the intestine, produces important changes in the nervous system, causing irritability, tetany, and spasmophilia; in the body skeleton, causing osteoporosis, deformities, and dwarfism; occasionally in the lens of the eye, causing opacities; and possibly in the blood, causing increased tendency to hemorrhage. As a result of fermentation of unabsorbed sugars, there is dilatation of the colon with resulting characteristic abdominal distention. Anemia of various types is common and in some cases there may be tongue lesions, skin lesions, and disturbance of water metabolism.

Within the past ten years the clinical picture of steatorrhea has been described in important publications by Fanconi in Switzerland; Thaysen in Denmark; Bennett, Hunter and Vaughan,[3] and Fairley and their respective collaborators in England; Moore and his collaborators[21] in Ireland; and by Holmes and Starr,[15] Mackie,[19] Pratt, Snell and Camp,[29] and Rhoads and Miller[28] in this country. This literature is widely scattered through clinical, pediatric, and special journals such as those devoted to tropical diseases. Relatively few papers have appeared in journals of roentgenology. It is not to be assumed, however, that the contribution of roentgenology in this disease is a minor one. On the contrary, a review of the literature as well as of my own experience indicates that the roentgen findings in idiopathic steatorrhea may be of great diagnostic importance. They may be summarized as follows:

* Read at the Thirty-ninth Annual Meeting, American Roentgen Ray Society, Atlantic City, N. J., Sept. 20–23, 1938.

| | |
|---|---|
| 1. In the small intestine | "Moulage sign," dilatation, segmentation. |
| 2. In the colon | Dilatation and redundancy |
| 3. In the gallbladder | Faint filling |
| 4. In the bony skeleton | Osteoporosis, deformity, and dwarfism |

In addition, 1 of my 6 cases showed an unusual type of gastric retention which will be described in detail in the case history. As a matter of fact, delayed gastric emptying, though not the rule, has been noted by Pillai and Murthi,[24] and Fanconi. These authors attribute this finding to gastric atony. Our case was almost certainly one of gastrospasm.

It should be noted that all the roentgen findings mentioned above are by no means present in every case. They vary in occurrence and in degree depending on the activity of the disease and the constitution of the individual.

Fig. 1. Normal jejunum. Note typical appearance of valvulae conniventes.

### SMALL INTESTINAL FINDINGS

Roentgenologically, the normal small intestine is characterized by the presence of circular folds (Kerkring's valves or valvulae conniventes) which begin in the second portion of the duodenum about 1 or 2 inches from the pylorus (Fig. 1). In the distal duodenum and upper half of the jejunum they are large and numerous, but from this point down to the middle of the ileum they diminish considerably in size. In the lower part of the ileum they almost entirely disappear (Gray[13]). Hence the contrast in the normal films between the herringbone appearance of the upper jejunum and the smooth outlines of the ileum. The caliber of the small intestine diminishes towards its end. A few measurements of normal films gave an average diameter of 1 inch in the jejunum and ½ inch in the terminal ileum.

In active steatorrhea the mucosal changes, as shown roentgenologically, are striking and once seen and understood are not likely to be forgotten. They take the form of coarsening or ironing out of the valvulae. Hence they are far more evident in the jejunum, and even in the distal duodenum, where the valvulae are normally more prominent, than in the lower small intestine. It is the first filled loops of jejunum,—corresponding roughly to the "second group of coils," according to Cole's[5] classification,—that are most strikingly involved. At times one obtains the impression that the wall outlines seem softer than normal. In advanced or acute cases the obliteration of the valvulae may be so complete that the roentgen appearance of the bowel resembles a tube into which wax has been poured and allowed to harden (Figs. 8, 9 and 10). In order to call attention to this characteristic wax model appearance of the jejunum in steatorrhea, I have suggested the descriptive term, "moulage sign." In my experience, the "moulage sign" furnishes the best visual evidence of the activity of the disease, appearing with the exacerbations of the steatorrhea and disappearing with its remissions. It may therefore serve as a useful aid not only in diagnosis but in prognosis as well.

In addition to the disappearance of the valvulae, there may be dilatation of the

small bowel lumen, and spasm with sausage formation or "segmentation." This phenomenon usually occurs lower in the gut, corresponding to the distal jejunum and ileum (Figs. 12, 13 and 14). Mackie has described clearly the isolated filled segments, the sausage-like appearance, and the localized pocketing, resembling at times a large diverticulum of the intestine. On the motor side, there is usually irregularity and delay in the rate of small intestinal evacuation. The total small intestinal emptying time is apparently delayed in the acute cases. However, a prolonged period of observation is not always necessary as oftentimes the diagnosis of steatorrhea can be made as soon as the first few loops of jejunum become visualized, that is, within fifteen minutes after the ingestion of the barium meal.

Credit for the original observation of these roentgen findings must go to Camp who, in association with Snell,[29] pointed out in 1934 that "alterations in the mucosal relief of the small intestine, especially the jejunum, consisting of smoothing of the contours of the lumen, obliteration of the usual markings of the valvulae conniventes, and clumping of the barium in elongated masses occurred in all of our (4) cases in which adequate roentgen observation was possible during the active stage of the disease."

The significance of this important contribution was not at once appreciated. For example, when Snell and Camp's paper was abstracted in the American Journal of Roentgenology and Radium Therapy there was no mention whatever of the jejunal findings, and Moore and his coworkers were unable to confirm these observations, possibly because they did not examine their cases in the phase of greatest activity. However, Mackie, Miller and Rhoads[20] and Golden[12] have amply corroborated the findings of Snell and Camp, and my own experience wholly agrees with Golden's that the roentgen examination may give the first indication of the existence of steatorrhea. Mackie found characteristic mucosal changes in 16 of 17 cases of sprue. Golden observed typical small intestinal changes in 7 of 11 cases of celiac disease, in 3 cases of chronic steatorrhea in adults, as well as in 2 other cases still under observation. He also reports the same findings in a case of steatorrhea due to lymphosarcoma of the jejunum and quotes a somewhat similar instance reported by Lehmkuhl. Feldman,[10] in his recent textbook, has published an excellent film showing the "moulage sign" in sprue.

Pendergrass and Comroe[22] have reported a case of chronic idiopathic adult tetany, the illustrations of which show a very striking "moulage" appearance in both the duodenum and jejunum. Their patient gave a history of long-standing diarrhea and showed definitely low calcium values.

Other authors whose observations indicate the importance of small intestinal changes in the roentgen diagnosis of steatorrhea are Fanconi, Gilbert and Babaiantz,[11] and Mach.[18] Although the loss of valvulae is not mentioned, other changes in morphology such as abnormal fluid levels, stippling and clouding, as well as altered or delayed motor activity are enumerated. Through the courtesy of Drs. Pillai and Murthi of Madras, India, I was able to secure a copy of their original roentgen study of tropical sprue hitherto apparently unavailable in its complete form in this country. Unfortunately, their work contains no specific reference to the morphology of the jejunum.

We do not yet know the exact nature of the pathologic changes which underlie the characteristic roentgen appearance of the small intestine in steatorrhea. Snell and Camp suggest the possibility of "an inflammatory condition with edema of the mucosa and infiltration of the walls." Mackie and his collaborators, in their study of sprue, mention, in addition to edema and infiltration, "a derangement of motor function and variations in muscular tone." As far as I know, no post-mortem studies of

cases of idiopathic steatorrhea are available for precise comparison with the roentgen findings.

In the series of cases reported in this paper, the diagnosis of steatorrhea was made twice from the "moulage" appearance of the small intestine. This was clearly evident in films brought by patients at their first visit. Of the total 6 cases, 4 showed classic "moulages." In 3 of these the proximal jejunum was most involved. In the next case the characteristic changes seemed to skip the first two jejunal loops but were marked in the succeeding convolutions. The 2 cases that did not show "moulages" were not carefully examined during the active phase of the disease. Detailed descriptions will be found in the case histories.

Perhaps a few words may be devoted to the question of specificity of these small intestinal changes. All the available evidence seems to show that they are directly associated with the presence of steatorrhea. This steatorrhea may be "idiopathic,"or, as pointed out by Bauer,[2] Golden, Fairley and F. P. Mackie,[8] and others, it may be the result of a variety of organic diseases that interfere seriously with the function of the lymphatics. All the conditions considered so far imply a failure of fat absorption. That other diseases not generally believed to be associated with fat malabsorption may produce similar small intestinal roentgen changes is suggested by Camp[4] who reports them in patients with pellagra, chronic pancreatitis, carcinoma of the head of the pancreas, and "acute gastro-enteritis." Obviously, what is now needed is a comprehensive investigation of a wide range of clinical conditions in which chemical studies of fecal fat are made simultaneously with roentgen observations of small intestinal morphology. However, in the present state of our knowledge it seems reasonable to assume that steatorrhea is the most common, if not the only, condition associated with the "moulage" appearance. In other words, for the time being, discovery of the "moulage sign" should suggest steatorrhea, leaving exceptions, if any, to be determined by further study.

### COLON FINDINGS

One of the most striking clinical features of steatorrhea is abdominal distention (Figs. 2 and 7). This is due to the dilatation of the colon with gas, and persists as long as the disease is active and the patient continues the unrestricted use of carbohydrates (Figs. 5 and 15). It is not the carbohydrates as such that are responsible for this condition because the stools never contain undigested starch particles, but rather the fermentation of sugars (glucose) which cannot be absorbed from the small intestine. Associated with the colonic dilatation is a moderate degree of redundancy. In my opinion, this is purely secondary to the distention and is not congenital in nature except by mere coincidence.

Roentgen evidence of colonic dilatation was described early in idiopathic steatorrhea. Thus, in the classic contribution of Holmes and Starr in 1929, it was noted in each of their original 5 cases. Practically all subsequent writers mention both colonic dilatation and redundancy. What has not been sufficiently stressed, in my opinion, is that steatorrhea seems to be the only form of grave chronic diarrhea in which the colon is dilated instead of being narrowed as it is in the organic dysenteries.

Bennett advances the hypothesis that the diarrhea disappears as the colon becomes increasingly atonic. My own experience does not, so far at least, confirm this viewpoint.

In the present series dilatation of the colon was demonstrated in 4 of the 6 cases. The capacity of the colon exceeded the normal 38 ounces (Kantor[17])in these patients. In the fifth case the colon was not dilated; it required only 31 ounces for complete filling. No accurate observations were made in the sixth patient.

Redundancy of the colon was noted in

5 cases. The distal colon was always the part involved.

### GALLBLADDER FINDINGS

In the present series, 3 of our cases were subjected to cholecystography during the acute manifestation of the disease. All 3 showed either no filling of the organ with the dyestuff (tetraiodophenolphthalein) or else a very faint visualization. In 1 of these cases it was possible to repeat the gallbladder study after clinical improvement was obtained following successful specific management. On this examination the gallbladder showed more normal filling and emptying.

The failure of the gallbladder to fill during the acute phase of steatorrhea seems thus to be an additional characteristic roentgen finding of the disease. This phenomenon has not been emphasized in the literature. As far as I can make out, it is recorded in only two articles. Radl and Fallon[27] mention non-visualization in their single case report of non-tropical sprue. Pillai and Murthi[25] report that 6 of 14 cases of tropical sprue showed non-visualized gallbladder "despite absorption of the dye from the intestines and its secretion by the liver." These authors believe that a definite gallbladder infection is present and that it plays an important rôle in this disease. As will be seen below, one of our cases, a male, gave a positive history of jaundice. In the other cases, even those in which faint filling was demonstrated, the usual signs and symptoms of gallbladder disease were quite absent.

Obviously, here is another field in which further studies should prove of great interest.

### BONE CHANGES

The stunted growth of celiac disease has been known since the time of Herter[14] (1908). According to Bennett, bone deformities in children were first reported in 1912 (McCrudder and Fales) and detailed roentgen studies were first made in celiac disease in 1927 (Lehndorff and Mautner, Parsons). In the same year bone changes in the idiopathic steatorrhea of adults were first described by Holst.[16] Since then others have reported many cases. Bennett and his coworkers made controlled roentgen studies and found "no instance of a normal skeleton" in their entire series of 15 cases. "The skeleton changes may take the form of dwarfism, dwindling of height, bone subcalcification, spontaneous fractures, osteomalacia and bending of bones, ununited epiphyses, deformity, or pain and tenderness over the bones and joints . . . Roentgenograms of bone sometimes show cross striations, denoting periods of increased calcification, of the juxta-epiphyseal region of the metaphysis (Moore, et al.)."

No special attention was paid to the bone changes in the present series of cases. One patient was a forty-five-year-old dwarf (height, 48 inches, weight, 55 pounds), another was short in stature (61 inches, 92 pounds, at age 55). The others were well grown, one young man of twenty-one being 72½ inches tall. Control films to demonstrate osteoporosis were made in only one instance and showed that slight rarefaction of bone density was present. The dwarf showed marked deformities in the pelvis and elsewhere in her skeleton.

### CASE REPORTS

Six cases comprise the present series. Five were private cases; one was observed in the wards of the Montefiore Hospital. Five of the 6 cases were born in this country (3 in New York, 1 in Chicago, 1 in Stamford), and 1 in Russia. None had ever resided in the tropics. Four of the patients were women, corresponding to the usual preponderance of females in this disease. Four of the patients were of asthenic habitus, the rest were classed as intermediates. Whether sthenics are affected seems yet to be determined.

All of the cases showed steatorrhea. Five of 6 cases had hypochromic anemia, and 1 of these also developed a hyperchromic anemia; 4 out of 5 showed slightly diminished or low normal blood calcium figures; 3 of 5 showed indicanuria; 2 of 3 showed a

flat sugar curve; 2 showed achlorhydria, 1 low gastric acidity, 1 normal acidity, and 1 high acidity. Two showed signs of tetany or gave a positive history of this condition. The patient with high acidity had a complicating duodenal ulcer and died as a result of perforation and hemorrhage of this lesion. The rest responded promptly to specific sprue management. In my practice, this comprises, briefly, the following procedures: Initial feeding period consisting exclusively of bananas and strawberries, non-sweetened tea and fruit juices *ad libitum;* when diarrhea and fermentation are controlled, progressive addition of protein foodstuffs; ultimate, very gradual, and extremely cautious addition of small amounts of carbohydrates and fats to tolerance; use of liver extract, in adequate doses, usually parenterally; administration of vitamins, calcium, and iron as needed; and use of blood transfusions as indicated.

Roentgenologically considered, 4 out of 4 carefully studied cases showed the "moulage" phenomenon. In 2 of these it was possible to roentgenograph the patients again after a period of treatment. Both of these cases showed definitely that the

TABLE I

CLINICAL FINDINGS IN IDIOPATHIC STEATORRHEA

| Case | Steatorrhea | Flat Sugar Curve | Anemia | Low Blood Calcium | Tetany | Indicanuria | Gastric Acidity | Habitus |
|---|---|---|---|---|---|---|---|---|
| I | + | + | + | +* | + | – | o | I |
| II | + | – | o | o | o | + | H | A |
| III | + | – | + | +* | o | + | o | A |
| IV | + | – | + | – | + | o | N | A |
| V | + | + | +** | + | o | o | + | A |
| VI | + | o | + | +* | o | + | S | I |

* Low normal
– No observation
o Absence of finding
\+ Presence of finding
** Changed from secondary to primary

H Hyperacidity
N Normal acidity
S Subacidity
A Asthenic
I Intermediate

TABLE II

ROENTGEN FINDINGS IN IDIOPATHIC STEATORRHEA

| Case | "Moulage" | Ileal Stasis | Dilated Colon (oz.) | Redundant Colon | Faint Gallbladder Filling | Delayed Gastric Emptying | Bone Changes |
|---|---|---|---|---|---|---|---|
| I | – | – | o (–) | + | – | o | + |
| II | + | – | + (96) | + | – | + | – |
| III | – | – | + (88) | + | – | + | – |
| IV | + | + | + (48) | + | + | o | – |
| V | + | Tr. | o (31) | o | + | o* | – |
| VI | + | + | + (60) | + | + | o | + |

* An overnight gastric residue was found with the stomach tube.

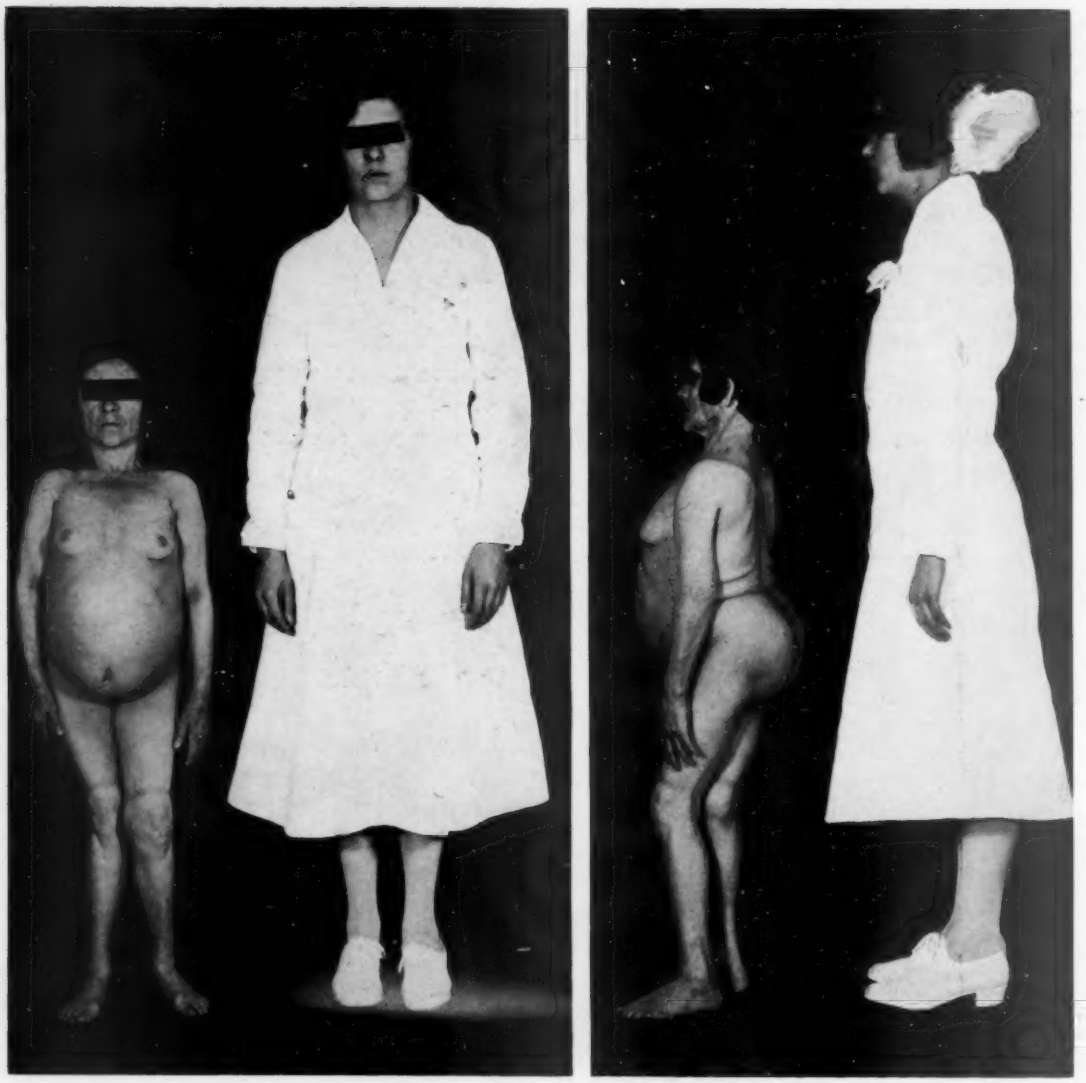

Fig. 2. Case 1. Idiopathic steatorrhea and dwarfism. Patient, aged forty-five, height 48 inches, weight 55 pounds, compared with normally developed woman. Note abdominal distention and skeletal deformities.

"moulage sign" had regressed or disappeared with the control of the steatorrhea. Three out of 3 patients showed ileal stasis; 4 out of 6 showed colonic dilatation, and 5 out of 6 showed colonic redundancy; 3 out of 3 showed faint filling of the gallbladder; 2 out of 6 showed delayed gastric emptying (a third showed transient delay with the stomach tube); and 2 out of 2 showed bone changes.

Synoptic charts of the chief clinical and roentgen findings in this series of cases are shown in Tables 1 and 11.

Case 1. Female, aged forty-five, born in Russia, was observed on the medical service at Montefiore Hospital from November 30, 1932, to September 19, 1933.

*History.* Diarrhea throughout childhood. At fourteen years there was a cessation of growth, the previous development having been normal. At this time there was, for one year, an exacerbation of diarrhea with ten to twelve watery stools daily, accompanied by weakness of legs and inability to walk, general debility, anemia, and attacks of tetany characterized by rigidity of fingers and general irritability. Then followed a free interval to five years ago when the meno-

pause occurred, the periods having previously been regular. Four years ago there was onset of palpitation, dyspnea, orthopnea, insomnia, anorexia, and weight loss. One year ago there was a profuse hemorrhage from a mucosal tumor of the right cheek (type undetermined) resulting in profound anemia with red blood cells under one million, hemoglobin under 10 per cent, requiring two transfusions, and complicated by ascites and edema of the legs.

*Physical Examination.* Stature dwarfed; height 48 inches; weight 55 pounds (Fig. 2). Bone deformities: bowing of long bones with epiphyseal broadening, rachitic chest, bilateral coxa vara and funnel pelvis; diffuse osteoporosis (Figs. 3 and 4). The abdomen was distended.

*Laboratory Findings.* Complete achlorhydria. Feces mushy, containing many fat globules staining with Sudan III. Blood sugar curve was as follows:

| | |
|---|---|
| Fasting | 99 mg. |
| One hour after 100 gm. glucose (in one dose) | 116 mg. |
| Two and one-half hours after 100 gm. glucose | 113 mg. |

This is a flat curve indicating failure of intestinal absorption. The blood calcium was 9.0 mg. (slightly below normal) on December 7, 1932, and 10.2 mg. on April 26, 1933 (normal 9.5 to 11.0 mg.). The blood phosphorus was slightly low, namely, 2.2 mg. (normal 2.5 to 4). The serum albumin was 4.5 per cent and the globulin 1.6 per cent (normal respectively, 4.5 and 2.5 per cent). The anemia was of the secondary type, probably the result of the previous hemorrhage. On the administration of iron, the blood figures rose from 40 per cent hemoglobin and 3,340,000 red blood cells to 85 per cent hemoglobin and 4,900,000 red blood cells.

Fig. 3. Case 1. Idiopathic steatorrhea and dwarfism. Note bone deformity (funnel pelvis) and osteoporosis.

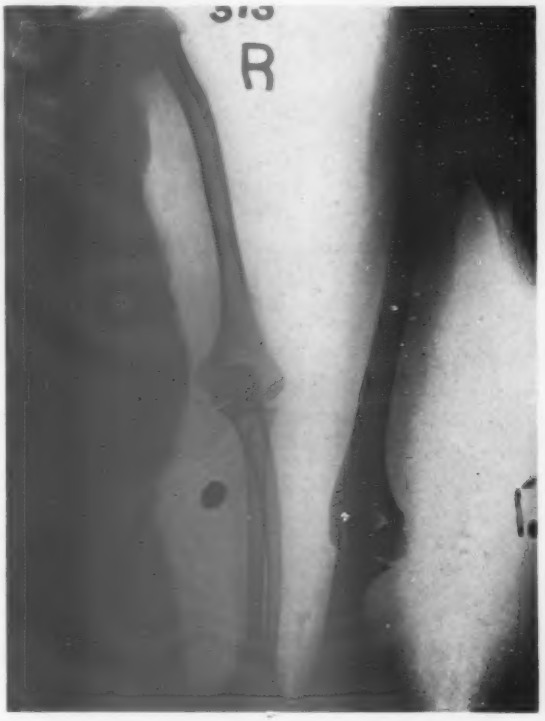


Fig. 4. Case 1. Idiopathic steatorrhea and dwarfism. Patient on left; normal control on right. Note deformity of humerus and osteoporosis.

*Roentgen Examination.* The small intestine was not studied during this hospitalization. The colon showed some redundancy. Examination of the small intestine during a "good period" in 1938 showed no "moulage sign."

*Course.* During this hospitalization the chief problem was the treatment of the anemia. However, on general hospital care, the abdominal distention diminished, and the stools lessened from three or four to two or three a day.

*Synopsis of Case History.* A case of probable steatorrhea in childhood resulting in dwarfism and bone deformities. During an "active period," fatty diarrhea, abdominal distention, and a flat sugar curve were demonstrated.

FIG. 5. Case II. Idiopathic steatorrhea. Roentgenogram after injection of air showing colonic dilatation and redundancy. Note distention of rectum.

CASE II. Female, aged fifty-five, single, came under observation April 5, 1933, complaining of one year's duration of flatulence, distention, cramps, occasional nausea, and frequent loose, frothy stools in the morning. There was an old history of duodenal ulcer dating back fifteen years. During the past ten years there was a steady loss of weight of 30 pounds.

*Physical Examination.* A short woman with prominent and distended abdomen. The height was 61 inches. The weight was 92 pounds, representing a weight deficit of 47 pounds or almost one-third of the normal body substance. The circumference of the abdomen was 27.5 inches (70 cm.). There was an old hypogastric scar (hysterectomy, appendectomy). The rectum was unusually capacious. Proctoscopy was negative. The tongue was normal.

*Laboratory Findings.* The urinary indican was much increased. The test meal figures, forty-five minutes after the standard test breakfast, were extremely high: free HCl 108, total acidity 114. The stools were large, watery, frothy, and showed fat clumps and fatty acid needles after heating with acetic acid. The hemoglobin was 91 per cent, the blood calcium 10.5 mg., and the phosphorus 3.3 mg. per 100 cc. (normal figures).

*Roentgen Examination, April 6 to 11, 1933.* The stomach showed hyperperistalsis and delayed emptying with residues at six hours on two occasions. The duodenal cap was enlarged. There was a question, on review of the films, whether an ulcer of the second portion could be diagnosed, but no definite niche was demonstrated. One or two proximal jejunal loops were dilated and smooth, but their appearance was distorted by the enormous dilatation of the colon. This held 96 ounces; the rectal distention was particularly well demonstrated (Fig. 5). The progress meal was eliminated in forty-eight hours with thirteen stools in the interval. At a subsequent examination at the Presbyterian Hospital (June 21, 1933) Dr. Ross Golden found that the ileum contained gas and showed fluid levels. The possible relation of these findings to the steatorrhea was not considered at that time. In short, the outstanding roentgen finding in this case was the great dilatation of the colon whose capacity was at least two and one-half times the normal. In addition, there was dilatation and segmentation of the proximal jejunum, and the position study showed fluid levels in the ileum.

*Course.* The stools and the abdominal distention improved on sprue management, but within three months the duodenal ulcer became active, bled, and perforated. An operation was performed on June 23, 1933, by Dr. F. B. St. John, who closed the perforation. The peritoneum showed an unusual blotchy and seared appearance, possibly the result of exuded acid gastric contents and blood. Despite all efforts, including six transfusions, the patient succumbed on June 30.

Autopsy revealed a large duodenal ulcer, 1½ inches in diameter, with an open branch of the pancreaticoduodenal artery in its base, the obvious source of the bleeding. The peculiar appearance of the peritoneum noted a week previously was no longer present. The spleen was small, a common finding in fatal cases of sprue.

*Synopsis of Case History.* A short woman, aged fifty-five, with an old history of duodenal ulcer, a ten years' history of unexplained weight loss, and a recent history of frothy diarrhea with marked abdominal distention. Death from perforation of, and hemorrhage from, the ulcer. The combination of duodenal

ulcer and steatorrhea is reminiscent of Radl and Fallon's case, and of the fourth case reported by Snell and Camp. As has been mentioned, it is possible that a primary organic disease may so seriously interfere with the intestinal lymphatics as to affect the absorption of fat.

Case III. Male, aged thirty, single, dentist, came under observation October 13, 1933, complaining of diarrhea and cramps.

*History.* Except for a transient summer diarrhea four years ago, the patient was relatively well up to two weeks ago. However, there was an unexplained weight loss from 152 pounds to 135 pounds in the past four years. For the past two weeks there were one or two foul, mushy stools in the morning, with abdominal cramps, distention, and flatulence.

*Physical Examination.* The patient was thin but full grown and of intermediate habitus. The height was $70\frac{3}{4}$ inches. There was a weight deficit of 33 pounds, the actual weight being 135 pounds. The abdomen was distended but was otherwise normal.

*Laboratory Findings.* The urine showed increased indican. The fasting stomach contained 40 cc. of old food residue. The test meal showed achlorhydria. The blood Wassermann and Kahn tests were negative. The hemoglobin was 84 per cent. The red blood cells were normal.

*Roentgen Examination, October 20 to 23, 1933.* The stomach showed a persistent prepyloric narrowing and irregularity (Fig. 6). There was a moderate gastric residue at five hours on two out of three observations. The colon showed a marked redundancy and dilatation. It required 88 ounces of opaque enema to reach the hepatic flexure, the cecocolon being filled with gas. Unfortunately, the small intestine was not carefully studied in this case. The few available small films failed to show a "moulage sign."

*Course.* The discovery of the gastric laboratory findings, the persistence of residues after a series of lavages, and the continuous weight loss led to a diagnosis of carcinoma of the stomach. Exploratory operation, January 17, 1934, at the Presbyterian Hospital, by Dr. A. O. Whipple, revealed no trace of organic disease even after the stomach itself was opened. In view of the subsequent findings, it is possible that the unexplained stomach condition might have been a manifestation of spasmophilia on the basis of a possible calcium deficiency. Unfortunately, no calcium studies were done in this case until considerably later.

Fig. 6. Case III. Idiopathic steatorrhea. Stomach, showing prepyloric deformity attributed to spasm. No organic lesion found at exploratory laparotomy and gastrotomy.

Following the operation, the course was rapidly downhill with progressive emaciation to 100 pounds by March, persistent diarrhea of three or four foul stools daily, development of secondary type of anemia, low grade fever (100° F.) and tachycardia (120), culminating on March 14, 1934, in an acute maniacal psychosis. By this time idiopathic steatorrhea was definitely diagnosed, the stools having shown fat indigestion on microchemical examination. The patient was admitted to the Montefiore Hospital and radical measures instituted, consisting of blood transfusions and rigid sprue diet. On March 27, 1934, the hemoglobin was 64 per cent, the blood calcium 9.1, and the blood phosphorus 3.6 (slight calcium deficiency).

On April 10, the status was: one or two bulky stools per day, mental confusion, anemia, tachycardia, with occasional fever rises to 101.8° F. maximum, hyperhidrosis and great prostration. The lowest recorded weight was 94 pounds, representing a weight deficit of 74 pounds, or 44 per cent of the normal body weight. The food intake was 2,900 calories. A body photograph taken May 11 shows the

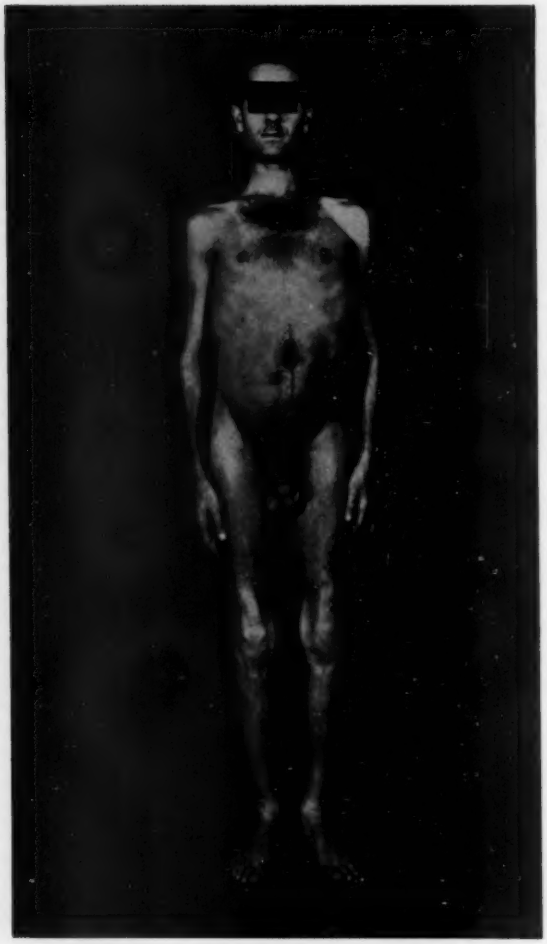

FIG. 7. Case III. Idiopathic steatorrhea. Photograph showing emaciation and abdominal distention with resulting ventral hernia in recent laparotomy scar.

state of nutrition as well as the abdominal distention which had resulted in the development of a ventral hernia at the site of the laparotomy scar (Fig. 7). From this point improvement was slow but steady so that on his discharge from the Montefiore Hospital on May 20, 1934, the patient weighed 116 pounds and was eating some carbohydrates and one-half pat of butter daily. Still further progress was made thereafter, but was interrupted by occasional recurrences of diarrhea and by the persistence of weakness. These symptoms were largely overcome in February, 1937, when liver extract by intramuscular injection was substituted for liver given by mouth (Dr. Winkelstein). At the present time, with the aid of liver by the parenteral route, the patient can handle a fairly liberal diet and is able to practice his profession on a full time basis.

*Synopsis of Case History.* A case of steatorrhea with marked malnutrition (44 per cent of normal body weight), achlorhydria, gastrospasm and pylorospasm leading to exploratory laparotomy and gastrotomy, anemia, psychosis, tachycardia, hyperhidrosis, and asthenia. Roentgen studies showed marked colonic dilatation and redundancy. A detailed study of the small intestine was not made. The available films failed to show a "moulage sign."

CASE IV. Female, aged forty-five, married, first came under observation February 13, 1937, complaining of recent hematemesis and epigastric pain.

*History.* In the past there had been no digestive disturbances save a tendency to constipation. The patient had never been pregnant; five years ago the uterus was found to be partly calcified. One and one-half years ago, following a cathartic, there was a severe epigastric colic with chills and cold sweat. The nature of this attack was not clear but in view of the subsequent discovery of a redundant colon, it was thought that a partial volvulus might have occurred. Strangely enough, the pains recurred late every afternoon following the original seizure. An ulcer was suspected but roentgen examination sixteen months ago failed to reveal it. The gallbladder, however, showed faint filling, and review of the original intestinal films showed a definite "moulage" appearance which was not recognized at the time. Ten months ago the pains were being treated by large doses of milk and cream, and six months ago the stools were observed to be large, greasy, and malodorous. Five months ago the pain increased and radiated to the back and began to come on at night. With this there were diarrhea distention, nausea, and vomiting, with a loss of 12 pounds in weight. The patient was now hospitalized and the roentgen examination was repeated. No ulcer was seen. The roentgenograms again showed a typical "moulage" which was once more overlooked. The stools, however, began to resemble butter and were found to contain 55 per cent fat in the dried state.

Four months ago there was a severe hematemesis with the hemoglobin dropping to 40 per cent. The source of the bleeding was not determined.

*Physical Examination, February 13, 1937.* Asthenic habitus with malnutrition of 31 pounds, the actual weight being 111 pounds. Pulse 144. Blood pressure 140/90. Gingivitis,

mild, with aphthous ulcer of left lip. Chest and abdomen normal.

*Course.* The patient was not seen after the February visit until November 7, 1937. Several attacks of pain had recurred in this interval. The hemoglobin varied between 45 and 60 per cent. The abdomen was distended every afternoon. The stools continued to be formed like butter until mid-October when they increased to six or eight per day and became watery. The fluid loss in the stools was tremendous, on one occasion the weight dropping 10 pounds in four days, to 96 pounds. On October 31, the patient was hospitalized. Feeding by mouth was stopped and intravenous glucose and saline was administered, 4,000 cc. being given in twenty-four hours.

On November 7, 1937, strict sprue diet was commenced (bananas and strawberries) with liver concentrate injected intramuscularly. Bleeding from the gums was troublesome and numerous subcutaneous ecchymoses were noted. One of these covered an area of about 6 inches in diameter. Cevitamic acid was given intravenously. On November 9 and 10, carpopedal spasm occurred and calcium gluconate was administered by the intramuscular route. Extrasystoles were observed and it was thought that these might represent an irritable myocardium due to calcium insufficiency. The hemoglobin dropped to 45 per cent on November 11, and the patient was again given a blood transfusion. In view of the very profuse perspiration, two teaspoonfuls of pure sodium chloride were given daily.

On November 13, the patient passed 74 ounces of alkaline urine, and on November 14, 104 ounces. This, in addition to the perspiration, caused great dehydration and asthenia. The renal fluid loss was combated by attempting to change the reaction of the urine. To this end, dilute hydrochloric acid and sodium acid phosphate were prescribed. By November 16, the polyuria, sweats, tetany, bleeding, and asthenia were under control. A rough estimate of the stools being passed at this time showed that they often weighed as much as 1 pound each in the fresh state.

On November 19 and 20, there occurred a striking change in the blood picture accompanied by fever (102° F.). The white cells increased to 30,000 and then to 38,000. The polymorphonuclears were 44 per cent, all segmented and without toxic granules. The clotting time was prolonged to one hour and ten minutes (normal upper limit sixteen minutes). This was interpreted as indicating a lack of fibrinogen, and representing a form of liver insufficiency. The leukocytosis was attributed to overstimulation of the bone marrow by the large injections of liver substance that had been given (Connery and Goldwater[6]). A transfusion of 600 cc. was followed by a reduction of clotting time to twenty minutes.

On November 21, edema of the tissues was observed, and the blood albumin to globulin ratio was found to be 4.2 to "trace." Following a transfusion, the albumin to globulin ratio became 4.2 to 0.025, the edema subsiding with diuresis. The stools still showed large numbers of fatty acid crystals. From this point there was gradual improvement, the weight reaching 102 pounds on December 6, the hemoglobin 69 per cent, and the red cells 3,500,000. On December 8, the patient was allowed out of bed and on December 12, the menses returned for the first time since the onset of the present illness. The diet at this time consisted of carbohydrates 450 grams (mostly bananas), protein 250 grams, fat 70 grams, total calories 3,400. Stool analysis: total fat 12.3 per cent, neutral fat 5.3 per cent, free fatty acid 7.0 per cent. This represents a normal splitting of fat, with a total output in proportion to the restricted fat in the diet.

On December 27, 1937, the patient was discharged from the hospital. While at home improvement continued. On January 6, 1938, examination of the dried stool showed 18.6 per cent fat on a moderately expanded diet. By February, the hemoglobin was 85 per cent, and the weight 125 pounds. On March 12, a melena occurred of undetermined origin but three days later the stool had regained its normal color.

On June 22, roentgen examination showed a practically normal jejunum, with only one loop in which the valvulae were diminished in depth and number. On July 29, the diet was: carbohydrates 233 grams, protein 172 grams, fat 88 grams, total calories 2,312. By August 19, the fat intake had been increased to 120 grams without any return of diarrhea. The hemoglobin was 92 per cent, and the weight 132 pounds. There are still occasional recurrences of abdominal pain which are partly relieved by belladonna.

*Roentgen Findings.* The first examination, October 23, 1935, by Dr. J. R. Freid, was made two years before the commencement of sprue treatment. In the erect posture the stomach

and duodenal cap are normal. The distal duodenum shows diminution in number of valvulae and increase in their size. The proximal jejunal loops are narrow and show coarse valvulae. The rest of the jejunum is dilated and shows widened and thickened valvulae. In the prone posture the second portion of the duodenum is widely dilated and shows a few thickened and coarse valvulae. The proximal jejunal loops are spastic, the second and third loops are dilated. All three loops show a typical "moulage" pattern. On April 29, 1936, the gallbladder shows a faint filling after the dye.

The second examination, October 15, 1936, by Dr. L. Jaches, was made one year before the commencement of sprue treatment. It shows a still more extensive "moulage" pattern.

The third examination, June 22, 1938 (J. L. K.), was made after seven months of sprue treatment, and when clinical recovery was well established. In one erect film a single proximal jejunal loop is dilated with some loss of valvulae. The rest of the jejunum is quite normal. The colon required 48 ounces to fill; the pelvic loop extends to the right. The gallbladder filling, though still faint, is more distinct than before. The organ appears quite atonic.

*Summary of Roentgen Findings.* In this case, the "moulage" appearance involved the proximal jejunum. This sign persisted apparently unchanged for at least a year before sprue treatment was begun. During this period the gallbladder showed faint filling. Seven months after the institution of specific sprue management, the "moulage sign" had practically disappeared. The colon was still dilated; the gallbladder filled somewhat more densely than at first, but was definitely atonic.

*Synopsis of Case History.* A case of steatorrhea complicated by severe abdominal pain, hemorrhagic diathesis, anemia, tetany, amenorrhea, disturbed water metabolism (polyuria, diaphoresis, edema), transient high leukocytosis, and loss of blood clotting power. Clinical recovery on sprue management. Roentgen study revealed persistent, typical "moulage" appearance of jejunum as well as faint filling of gallbladder, both of which signs improved with clinical recovery. The colon was dilated and redundant. The hemorrhages into the digestive tract were unusual and recalled somewhat the case of hemorrhage into the jejunum reported by Holst.

CASE V. Female, aged twenty-seven, married, came under observation January 29, 1938, complaining of diarrhea, abdominal pain, malnutrition, and gas distress.

*History.* Constipation was present from childhood to ten years ago when the bowels began to move spontaneously. Five years ago there began a progressive weight loss, the cause of which was not apparent to the patient. The weight dropped from 128 to 113 pounds in this interval. Milk and eggs used for fattening caused gas distress. Three years ago a sudden diarrhea developed and lasted four months. The stools numbered four to five a day, often reached a pint in size, and were mushy, or watery and frothy in consistency, with a penetrating odor. Accompanying this diarrhea there was epigastric pain, nausea, vomiting, and much flatulence. Edema of the feet occurred then, and again two months ago. During the past two years diarrhea recurred twice, the last attack beginning one month ago. For six months the gums had been bleeding moderately, and for four months there was anorexia, increasing weakness, profuse sweats, and persistent weight loss. Roentgen examination made by different roentgenologists in May, 1935, and on January 24, 1938, five days before the first visit, showed a definite "moulage sign," the significance of which had not been appreciated.

*Physical Examination.* Asthenic habitus. Malnutrition of 23 pounds (actual weight 105). The pulse varied between 112 and 92. The blood pressure was 94/60. The tip of the tongue was tender but appeared normal. The abdomen was tender in the epigastrium but there was no distention.

*Laboratory Findings.* The feces on mixed diet were mushy, pale yellow, acid, and had a pungent odor. There were no undigested meat fibers, nor free starch cells by the iodine test. After heating with acetic acid, cooling and staining with Sudan III, there were numerous fat clumps and needle crystals. The fasting stomach contained old food residue; free HCl was present. The delayed gastric emptying shown by the stomach tube was presumably a transient condition as it was not confirmed by subsequent roentgen study or by the clinical course. A test meal was not done. The urine was normal; the indican was not increased. The blood was examined by Dr. N. Rosenthal:

| | February 8, 1938 | August 26, 1938 |
|---|---|---|
| Hemoglobin | 65% | 90% |
| Color index | 0.79% | 1.1 % |
| Red blood cells | 4,110,000 | 4,100,000 |
| White blood cells | 5,700 | 6,600 |
| Platelets | 430,000 | 240,000 |
| Polys. staff | 7.0 % | 2% |
| Polys. segmented | 58.0 % | 60% |
| Polys. eosinophile | 1.0 % | 3% |
| Polys. basophile | 0.5 % | 2% |
| Lymphocytes | 25.0 % | 26% |
| Monocytes | 8.5 % | 7% |
| Reticulocytes | 0 % | |
| Relative cell volume | 32.55% | |
| Relative plasma volume | 67.45% | |

The count of February 8 was reported: "A moderately severe hypochromic anemia. The red cells show moderate anisocytosis and slight poikilocytosis with some variation in size"; and that of August 26 was reported: "A slight hyperchromic anemia. The red cells appear uniform in size and are well filled with hemoglobin with, apparently, no central pallor. The color index is increased. No nucleated red cells seen." Thus, in this case, the blood showed an interesting change from a secondary to a primary form of anemia, a variability which has been observed by previous writers (Thaysen, Bennett).

Fig. 8. Case v. Idiopathic steatorrhea. Jejunum, showing typical "moulage sign" in first filled loops. Film taken three years before commencement of specific treatment. (Courtesy of Dr. W. W. Maver.) Compare with Figures 9, 10 and 11.

Fig. 9. Case v. Idiopathic steatorrhea. Jejunum, showing typical "moulage sign" in erect posture. Film taken immediately before commencement of specific treatment. Compare with Figures 8, 10 and 11.

The blood sugar curve was also studied by Dr. Rosenthal. The normal increase after the two doses of glucose is 30 mg. per cent. The figures in this case were as follows:

| | Jan. 31 mg. | May 9 mg. | Aug. 26 mg. |
|---|---|---|---|
| Fasting specimen | 79.5 | 90.36 | 120 |
| One-half hour after 50 gm. glucose (1st dose) | 68.8 | 116.20 | 144 |
| One-half hour after 50 gm. glucose (2nd dose) | 79.0 | 75.20 | 115 |

All these curves are typical of sprue. The first is quite flat indicating lack of absorption from the intestinal tract; the rest show slight temporary rises but soon descend to a level below that of the fasting state. In general, the blood sugar increases as the patient improves. On January 28, the blood calcium was 8.8 mg. per 100 cc., indicating the presence of a calcium deficiency.

Fig. 10. Case v. Idiopathic steatorrhea. Jejunum, showing typical "moulage sign" in prone posture. Film taken immediately before commencement of specific treatment. Compare with Figures 8, 9 and 11.

*Roentgen Findings.* The first examination, May 27, 1935, by Dr. W. W. Maver, was made almost three years before the commencement of sprue treatment. The duodenum shows slight dilatation of the second and third portion, the valvulae being coarser and fewer than normal. The three uppermost (proximal) loops of jejunum show typical "moulage," with some dilatation and spasm (Fig. 8). The lower loops of jejunum show a ladder pattern. The stomach is empty at five hours. The colon shows no abnormality.

The second examination, January 24, 1938, by Dr. M. Friedman, was made a week before the commencement of sprue treatment. The second portion of the duodenum shows some puddling and fair "moulage." The jejunum shows typical "moulage." The stomach is empty at five hours. The colon is normal.

The third examination, February 1 and 4, 1938 (J. L. K.), was made immediately before the commencement of sprue treatment. The stomach and duodenal cap are normal. There is some dilatation of the second and especially the third portion of the duodenum, and the valvulae are coarse and thickened. The upper jejunal loops show typical "moulage sign" (Figs. 9 and 10). At twenty-five minutes the jejunum is filled well down into the left iliac fossa; the lower loops show practically no "moulage." At one hour there is a slight remaining "moulage" in the jejunal loops in the left upper quadrant. At two hours the "moulage" has almost disappeared, the jejunal loops being practically empty. At three hours the stomach is empty. At five hours the ileum is practically empty (normal emptying time nine hours) but a few flecks of barium persist to nine hours. Opaque enema: Only 31 ounces were required to fill to the cecum. There is no dilatation of the colon and no redundancy. Cholecystography, February 10 and 11: Gallbladder shows faint filling but empties normally after the fat meal.

The fourth examination, March 9, 1938 (J. L. K.), was made after thirty days of sprue treatment. The stomach and duodenum are normal. The "moulage sign" has practically disappeared, the mucosal folds of the jejunum being only slightly thicker than usual, but the general morphology is almost normal (Fig. 11).

*Summary of Roentgen Findings.* This case showed a typical "moulage" of the proximal

Fig. 11. Case v. Idiopathic steatorrhea. Jejunum, showing rapid disappearance of "moulage sign." Film taken after thirty days of specific treatment. Compare with Figures 8, 9 and 10.

jejunum presumably persisting over a period of three years before the commencement of specific sprue therapy. The stomach emptying was normal. There was no ileal stasis and no colonic dilatation or redundancy. The gallbladder showed faint filling. Thirty days after the commencement of sprue therapy the "moulage sign" had almost entirely disappeared.

*Course.* On February 7, sprue management was begun and by the end of the month the strength was greater and the weight had reached 110 pounds. By March 19, the hemoglobin had become 86 per cent, a gain of over 20 per cent in one month; the weight was 114 pounds; the stools were formed and reduced to one a day, and no longer showed fat on microchemical examination; the pulse had slowed to 74 per minute. In April, leg pains had become prominent but there was no evidence of Chvostek or Trousseau phenomenon. Vitamin B therapy did not bring relief. Cheese was added to the diet but this did not seem to supply the calcium lack since the leg pains persisted. Calcium therapy was begun in June and proved successful. Examination of the eyes on June 29, 1938, by Dr. R. K. Lambert failed to show any lenticular opacities under the slit lamp. On August 18, examination of the fecal fat in the stools collected during three days of standard Schmidt diet in which the fat was 142 grams per day, showed a fat loss of 7.3 per cent which is well within the normal limits of 5 to 8 per cent. At this time the patient's daily diet contained a fat intake varying from 50 to 155 grams. On August 26, the blood report showed the development of a mild hyperchromic anemia. Associated with this was a recurrence of weakness, anorexia, nausea, and some loss of weight. Liver injections, which had been discontinued for some time, were resumed and are being given at the present writing (September, 1938).

*Synopsis of Case History.* A case of steatorrhea in a young woman, with diarrhea, malnutrition, hypochromic anemia changing to a hyperchromic form while under treatment, leg pains, low blood calcium, and a typical flat sugar curve. The "moulage sign" was demonstrated three times in a period of three years before specific treatment was started, but practically disappeared after a month of sprue management. The gallbladder showed faint filling.

Case vi. Male, aged twenty-one, single, came under observation June 28, 1938, complaining of abdominal pain, gas distention, and occasional diarrhea.

*History.* There was a tendency to constipation since childhood. Thirteen years ago osteomyelitis of both legs was operated on. Eight years ago onset of lower abdominal colics relieved by appendectomy five years ago. From six to two years ago cramps in the legs were present. Four years ago anorexia for one year, and onset of some belching and vague abdominal distress with occasional nausea and vomiting. Three years ago onset of attacks of diarrhea with five or six large, watery stools daily, the attacks recurring every two weeks. Two years ago onset of spells of chills and fever recurring every two to three months, with abdominal cramps usually relieved by the stools, much foul flatus, and persistent abdominal distention. The stools were large but apparently not oily, soapy, or frothy. Six months ago the tongue became sore and remained so for three months. Two months ago there was an attack of jaundice, preceded by fever, which lasted three weeks. The jaundice was assumed to be catarrhal but its real significance was not determined.

*Physical Examination.* Intermediate habitus. Malnutrition of 35 pounds (actual weight 132 pounds, height 6 feet ½ inch). The tongue was red in the center, the follicles beneath the tongue were increased in size. The teeth showed many filled cavities. The patient had much more dental caries than his sisters. There was a dark pigmentation of the operative scars on both legs and a patch of dark scaling eruption on the right leg strongly suggesting a pellagrous lesion. The abdomen was distended and tympanitic, the circumference of the midabdomen with the patient standing being 30¼ inches. The capacity of the rectum was much increased as shown by finger palpation. The pulse was 74, the blood pressure 94/60.

*Laboratory Findings.* The urine showed increased indican. The test meal figures were free HCl 13, total acidity 29, indicating a diminished gastric acidity. The stool on unselected diet was semiformed, gray, sour smelling, and acid in reaction. On heating with acetic acid, cooling, and staining with sudan III, there were numerous fat clumps and fatty acid crystals. The patient was then given the standard Schmidt intestinal diet for three days, the fat intake being 142 grams per day. The dried

Fig. 12. Case vi. Idiopathic steatorrhea. Film taken one-half hour p.c. First loop of jejunum normal. Second loop shows fair "moulage" with few coarse valvulae. Third loop shows enormously dilated segment resembling a large diverticulum (Mackie). Distal jejunum empty. Compare with Figures 13 and 14.

stools collected from the three day period contained 32 per cent fat (normal average 17 per cent).

The blood studies by Dr. N. Rosenthal showed the following:

| | July 5 | August 25 |
|---|---|---|
| Hemoglobin | 73% | 68% |
| Color index | 0.77% | 0.78% |
| Red blood cells | 4,710,000 | 4,370,000 |
| White blood cells | 4,500 | 8,200 |
| Platelets | 220,000 | 240,000 |
| Polys. staff | 5 % | 2 % |
| Polys. segmented | 35% | 40% |
| Polys. eosinophile | 2 % | 0 % |
| Polys. basophile | 0 % | 3 % |
| Lymphocytes | 52% | 48% |
| Monocytes | 6 % | 7 % |
| Reticulocytes | 0.5 % | |

The first report indicates a slight depression in hemoglobin and a tendency to leukopenia with a lymphocytosis. On the same date the blood calcium was 9.1 mg. per 100 cc. and the phosphorus 3.26 mg. The second blood count shows a slightly increased hypochromic anemia. The blood sugar curves were as follows:

| | July 5 | August 25 |
|---|---|---|
| Fasting | 101.5 mg. | 112 mg. |
| One-half hour after 50 gm. of glucose (1st dose) | 136.5 mg. | 180 mg. |
| One-half hour after 50 gm. of glucose (2nd dose) | 115.0 mg. | 160 mg. |

The first curve may be considered a low normal. The second is quite normal.

*Roentgen Examination, June 30, 1938* (J. L. K.). The stomach and duodenal cap are normal. The rest of the duodenum is dilated but the valvulae conniventes are normal. The proximal loop of jejunum runs vertically downward from the duodenojejunal flexure and shows normal valvulae. The second loop runs horizontally to the left for 4 inches, stopping to the right of the spine. In this loop the valvulae are very few and large. The third loop turns sharply back crossing the spine almost horizontally and ending abruptly 2 inches to the left of the vertebral column. This loop is

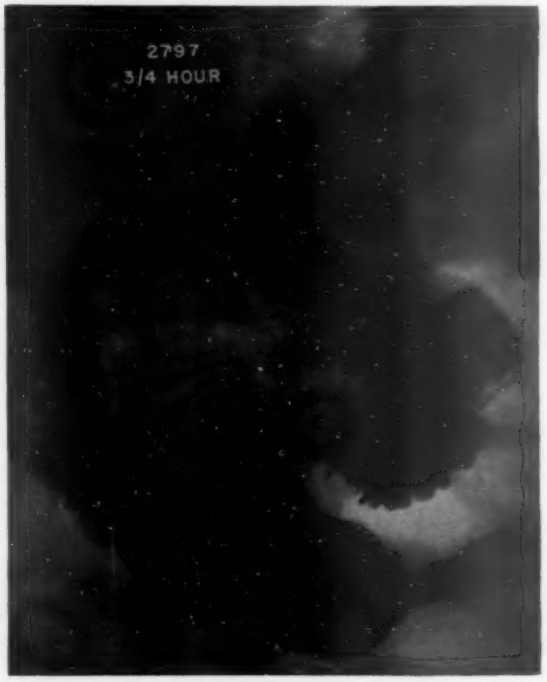


Fig. 13. Case vi. Idiopathic steatorrhea. Film taken three-quarters of an hour p.c. Third loop of jejunum beginning to empty distally with apparent relief of localized spasm. Compare with Figures 12 and 14.

greatly dilated, being 4½ inches long and from 2¼ to 2½ inches in diameter. It is entirely devoid of valvulae. It seems to act as a temporary reservoir, remaining unchanged for fifteen minutes, at the end of which time it begins to empty into the adjacent jejunum which is of normal caliber but shows very few, coarse valvulae (Figs. 12 and 13). The entire picture is reminiscent of the "large diverticulum of the intestine" described by Mackie.

One hour p.c. the stomach still contains some barium. The dilated jejunal loop is much smaller. The jejunum is now filled distally in the left midabdomen and in the left iliac fossa. These newly filled loops show dilated segments separated by spastic contractions (Fig. 14). Two hours p.c. the stomach and the upper jejunum are practically empty. The barium is now almost all concentrated in dilated, smooth-walled segments of terminal jejunum and ileum occupying the left iliac fossa, the upper pelvis and the right iliac fossa. At five hours all the barium is in the ileum which is moderately dilated, and the cecum has just begun to fill. Between this and the eight-hour observation there is not much change, but at nine hours progress has been resumed. The terminal ileum shows only a small residue and the colon has been filled in irregular fashion to the splenic flexure. There is considerable gas at the hepatic flexure and in the descending and iliac colon. At twenty-four hours the dilatation and redundancy of the distal colon are quite evident. Opaque enema: Sixty ounces required to fill to the cecum. The colon is dilated; there is a complete loop of the descending portion (Fig. 15). The gallbladder shows extremely faint filling.

Fig. 14. Case VI. Idiopathic steatorrhea. Film taken one hour p.c. Third loop of jejunum has emptied further. Distal loops show typical dilated segments separated by spastic areas. Compare with Figures 12 and 13.

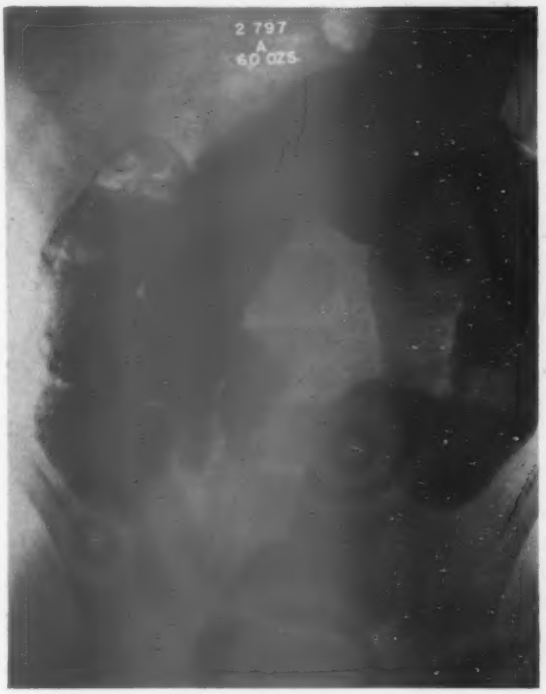


Fig. 15. Case VI. Idiopathic steatorrhea. Opaque enema showing colonic dilatation and redundancy. It required 60 ounces to fill to the cecum. The normal colon holds 38 ounces.

*Bone Study.* In comparison with a sister two years younger than the patient, the bones of the forearm and hand show a slight though definite osteoporosis.

*Summary of Roentgen Findings.* In this case the "moulage" was atypical and involved the lower rather than the upper jejunal loops. There was considerable dilatation and spasm of the distal jejunum and the proximal ileum, with stasis in the involved loops. The redundancy of the colon and the dilatation were considerable. The gallbladder practically failed to fill.

*Course.* Sprue diet and management was begun on July 8, 1938. On July 16, without apparent cause, there was anorexia, weakness, and moderate fever. Two days later, following the unauthorized ingestion of cake and chocolate candy, the patient developed severe cramps and a definitely palpable spastic colon which persisted until relieved by belladonna on July 25. The weight dropped to 128½ pounds on July 19. By August 5, the pigmented lesion of the left leg had completely disappeared and the circumference of the midabdomen had diminished to 28¾ inches. The stools were well formed and practically odorless. In view of the drop in blood pressure (80/50) fresh whole suprarenal substance was begun by mouth on this date. By August 25, the weight had increased to 139 pounds, and the blood pressure to 98/58. The strength was much greater than previously and the appearance much brighter. The diet now included considerable carbohydrates, but no free fat (no butter, cream, eggs, or fat meat). The anemia still constitutes a problem as it has developed despite the administration of liver and iron. At the present writing (September, 1938), it is planned to increase the iron intake. The weight is 140½ pounds.

*Synopsis of Case History.* A case of idiopathic steatorrhea in a well-grown young man, characterized by malnutrition, progressive secondary anemia, occasional fever and intercurrent jaundice, abdominal cramps, distention, sore tongue, leg pains, moderate osteoporosis, pellagrous skin lesions, atypical "moulage sign" with segmental dilatation and spasm in lower jejunum and ileum, dilated redundant colon, and almost complete failure of gallbladder filling. General improvement, except for anemia, and rapid weight gain on sprue management.

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## SUMMARY

1. In idiopathic steatorrhea there are characteristic roentgen changes in the small intestine, colon, gallbladder, and bony skeleton. These findings are not constant nor all present in every case but vary in their degree and distribution depending on the activity of the disease and the constitution of the individual.

2. The changes in the small intestine are most apparent in the jejunum. These consist of variations in tone, caliber and motility, and particularly in the diminution or complete disappearance of the distinctive valvulae conniventes.

3. The term "moulage sign" is suggested as a means of calling attention to the striking appearance of the upper jejunum when the valvulae conniventes are missing and the lumen is filled smoothly as though wax had been poured into it. Since this peculiar appearance seems to vary directly with the intensity of the steatorrhea, the "moulage sign" may have practical value in both diagnosis and prognosis.

4. The characteristic findings in the colon are marked dilatation, often associated with redundancy. Idiopathic steatorrhea is probably the only form of grave chronic diarrhea in which the colon is dilated instead of contracted.

5. The characteristic finding in the gallbladder is faint filling. The exact significance of this is not yet apparent.

6. The characteristic findings in the bony skeleton are dwarfism, deformity, and osteoporosis.

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DISCUSSION

Dr. Ross Golden, New York. Dr. Kantor has prepared for us a very thorough and interesting résumé of a very interesting condition. This you will realize even more when you have the opportunity to go over his complete paper, as I have done.

I wish he had been able to resist his impulse to give us a new name for the roentgen appearance of the jejunum in this condition. The term "moulage" I think could hardly be applied to the changes which are visible on the film in the cases of infantile celiac disease which I have seen, although the duodenal and jejunal mucosa is definitely abnormal, nor could this term be reasonably applied, I think, to early jejunal changes in adults. It seems to me that our thinking might be a little more direct and clear if we stick to medical description.

However, Dr. Kantor has brought out many very interesting points which stimulate discussion, all of which obviously cannot be taken up.

Steatorrhea and allied conditions, as he has mentioned, are the result of a lack of some specific substance or substances which may possibly be different in different cases. I have been in the habit of applying a broad general term, "deficiency states," to these conditions, which may or may not be a good term.

I have seen 2 cases in which steatorrhea apparently followed primary disease of the mesenteric lymph vessels and lymph nodes. In 1 case, it was followed by a complete clinical picture of sprue, including the tongue changes. In another instance, a too rigid duodenal ulcer diet was followed by diarrhea and roentgen changes in the jejunum which led to an independent interpretation by the clinician, and from the roentgenograms by me of a deficiency

state. The high vitamin diet upon which the patient was promptly placed was followed by complete cessation of the symptoms and a restoration to normal of the appearance of the jejunum. This patient was sent in specifically for examination of the small intestine on account of diarrhea, because our clinicians now realize that the small intestine may be the cause of diarrhea.

In advanced cases of steatorrhea, the dilatation and fluid levels which appear in the small intestine may suggest, on the plain films without the barium, the possibility of intestinal obstruction.

In 1934, Gutzeit and Kühlbaum described small intestinal changes in icterus which are similar to those now under discussion; that is, slight dilatation, slowing of motility and coarsening of the mucosal folds. Their work on animals and their clinical experiments seem to indicate that the disturbance in the small intestine could be relieved by the administration of bile by mouth; hence they attributed the changes to the absence of bile in the intestine. Some German writer, I have forgotten who he was, on the basis of this work made the suggestion that a diagnosis of obstruction in the biliary tract could be made from the demonstration of these changes in the small intestine. I do not believe that is justified because the same abnormalities of the small intestine are seen in a number of other conditions.

In regard to healing, my experience has been a little different from that of Dr. Kantor. I have seen only 3 or 4 well-developed cases such as he has shown, but in none of them has the jejunum returned completely to normal. In fact, in the cases he showed, I would not think that the mucosal folds of the jejunum after treatment had been restored completely to normal. I would agree rather with the statement of Snell and Camp in their paper that treatment was followed by a restoration *toward* normal.

Dr. Kantor correctly stated that knowledge concerning these conditions is quite limited at the present time, and for that reason we should not go too far in our interpretation. I like to limit myself to the mere statement that probably some kind of a deficiency state is present, and the clinician will have to go farther in finding out just what it is. I think probably one of the important lessons that we can learn from such presentations as Dr. Kantor has made is the great importance of stopping to look at the small intestine.

DR. KANTOR (closing). Whether the term "moulage sign" is accepted or not is really not important. What I hoped to stress is that the roentgenologist, by recognizing this condition, is now in position to make the diagnosis. Indeed, he can be the first to do so as shown by the fact that in 2 of my cases the diagnosis of steatorrhea was made from films brought to the office by patients.

Owing to the lack of fundamental knowledge of this group of diseases nomenclature is difficult. Thus one could object to calling this a "deficiency state" because too much emphasis would then be placed on the lack of vitamins. One must remember that the condition cannot be cured by just *adding* vitamins to the diet. In fact, in order to help the patient one must first *subtract* from the diet by excluding fat and ordinary carbohydrates. Only banana sugar is assimilated and in the acute stages this fruit constitutes practically the entire diet.

In the tuberculosis cases, one may theorize as follows: There must be a certain number of individuals, be they tuberculous or not, who have a limited fat tolerance. If one overfeeds them with milk or butter, one may reach the same stage that one might in the case of certain duodenal ulcer patients that are overfed with milk and cream. Once the threshold of tolerance is overstepped, there results the clinical picture which we have seen. Such cases of tuberculous involvement of the lacteals were described by Fanconi in Switzerland.

Dr. Golden mentioned the fact that there was no ulceration. This is not a disease of the mucosa in the sense of an ulceration. It is a disease of the absorbing components, mucosal or lacteal, as the case may be.

The object of this preliminary report is merely to focus the attention of roentgenologists on this interesting condition so that they may be able to recognize it when the opportunity arises.

Vol. 41, No. 5

# CONGENITAL NEUROSYPHILIS

## REPORT OF A CASE WITH UNUSUAL ENCEPHALOGRAPHIC CHANGES*

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THE case of congenital syphilis with syphilitic meningitis here presented is considered to be of interest because of the following features:

1. The survival of a patient with symptoms of such severity that the initial prognosis was considered hopeless.
2. The response to therapy with a relatively new arsenical—mapharsen.
3. The growth of brain tissue following apparent cortical atrophy as demonstrated by encephalography.
4. The surprising degree of mental and physical function which has resulted under continuous antisyphilitic therapy.

### CASE REPORT

*History.* The patient was a white female infant admitted at the age of ten weeks with the complaints of "holding the head back" and "snuffles" of eight weeks' duration. She was the result of the first pregnancy of parents who denied syphilitic infection by name or symptoms, although subsequent tests showed both parents to have a positive blood Hinton test. There was nothing unusual in the birth history or the early post-natal course. The birth weight was 7 pounds and the weight on admission was 10 pounds. A rash of vesicular nature appeared two weeks before admission, and was first noticed on the left side of the face and then on the palms and soles. Red "blotches" on the back appeared a few days before admission.

*Physical Examination.*

*General appearance:* A fairly well developed and nourished white female infant lying in marked opisthotonos position (Fig. 1).

*Skin:* There were brownish-pink papules 1–3 cm. in diameter distributed thickly over the back and dorsal surface of the legs. The skin of the hands and feet was thickened, dry and scaling, and there were deep, bleeding fissures in the interdigital webs.

*Measurements:*

| | | |
|---|---|---|
| Body length | 18 | inches |
| Circumference of head | 15 | inches |
| Circumference of chest | 15 | inches |
| Circumference of abdomen | 15.5 | inches |

*Head:* The anterior fontanelle was tense but not bulging. The forehead was high and prominent, the bridge of the nose was depressed, and there was a profuse bloody nasal discharge.

FIG. 1. Patient at age of two months.

*Eyes:* The pupils reacted sluggishly to light. There were minute scars on the posterior surface of the left cornea. The iris of the right eye was irregular on the medial side, due to adhesions between the lens and the iris.

*Lymph nodes:* All superficial lymph nodes were enlarged.

*Heart and lungs:* Normal.

*Abdomen:* The abdomen was markedly distended. The spleen was palpable 3 cm. below the costal margin on the left. The liver was palpable 5 cm. below the costal margin on the right.

*Neurological Examination.* The neck and back were rigid and arched in the opisthotonos position. Kernig's sign was negative. The deep tendon reflexes were present and equal but sluggish.

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*Hematology.* Hb, 5.5 grams; erythrocytes, 1,630,000 per cu. mm.; leukocytes, 17,300 per cu. mm.

*Urinalysis.* Negative.

*Blood Hinton.* Positive.

*Tuberculin Test.* Mantoux (0.1 mg. O. T.), negative.

*Cerebrospinal Fluid.*

| | |
|---|---|
| Initial pressure | 170 mm. water |
| Appearance | Xanthochromic |
| Total protein | 258 mg. per cent |
| Sugar | 20 mg. per cent |
| Total leukocytes | 440 |
| Mononuclear cells | 85 per cent |
| Polymorphonuclear cells | 15 per cent |
| Culture | No growth |
| Wassermann reaction | Positive |
| Colloidal gold test | 4553210000 |

*Roentgen Findings.* The changes in the long bones were reported as diagnostic of congenital

Fig. 2. Patient at age of eighteen months.

syphilis. Encephalograms were not done at this time.

*Therapy.* Therapy was started with a mercury binder one day after admission. One week later 8 mg. of hypoloid bismuth was injected intramuscularly and was repeated three days later. Two days following the last injection of bismuth, intravenous mapharsen was started in a dosage of 0.25 mg. per kilogram of body weight. It was given bi-weekly and the dose was increased 0.25 mg. at each dose to a maximum of 1.0 mg. per kilogram. A total of twelve injections was given in this course, and the mercury binder was continued for its duration.

The hypoloid bismuth was then resumed with injections of 10.0 mg. intramuscularly weekly for eight weeks. This was followed by twelve weekly injections of mapharsen intravenously in a dosage of 1.0 mg. per kilogram of body weight. The last course of bismuth was then started in the form of bismuth salicylate in oil intramuscularly in a dosage of 0.4 cc. weekly for eight weeks. Following this the treatment to date has consisted of alternate courses of acetarsone and mercury inunctions for a total of four courses. Each course of acetarsone consisted of nine weeks of daily oral dosage of 5.0 mg. per kg. of body weight the first week, 10.0 mg. per kg. the second, 15.0 mg. per kg. the third and 20.0 mg. per kg. from the fourth to the ninth week. A course of mercury inunctions consisted of the application of 1.0 gm. of 30 per cent mercury ointment to the skin daily for one month.

*Course.* During the first two weeks of hospitalization the initial symptoms became worse, the opisthotonos more pronounced, and in addition there was mild vomiting, diarrhea and elevation of temperature to 102° F., followed by the loss of 1 pound in body weight. For these reasons it was decided to give intravenous mapharsen. The response to this treatment was dramatic. The temperature dropped to normal in five days, no further weight loss occurred, the vomiting and diarrhea ceased, and the skin lesions and the bloody nasal discharge rapidly disappeared. However, the opisthotonos did not completely disappear until three weeks after the mapharsen was started. One week after the twelfth injection of mapharsen, exexamination of the cerebrospinal fluid showed the following:

| | |
|---|---|
| Initial pressure | 90 mm. water |
| Appearance | Clear |
| Total protein | 96 mg. per cent |
| Sugar | 31 mg. per cent |
| Total leukocytes | 12 mononuclear cells |
| Colloidal gold test | 2100000000 |
| Wassermann reaction | Positive |

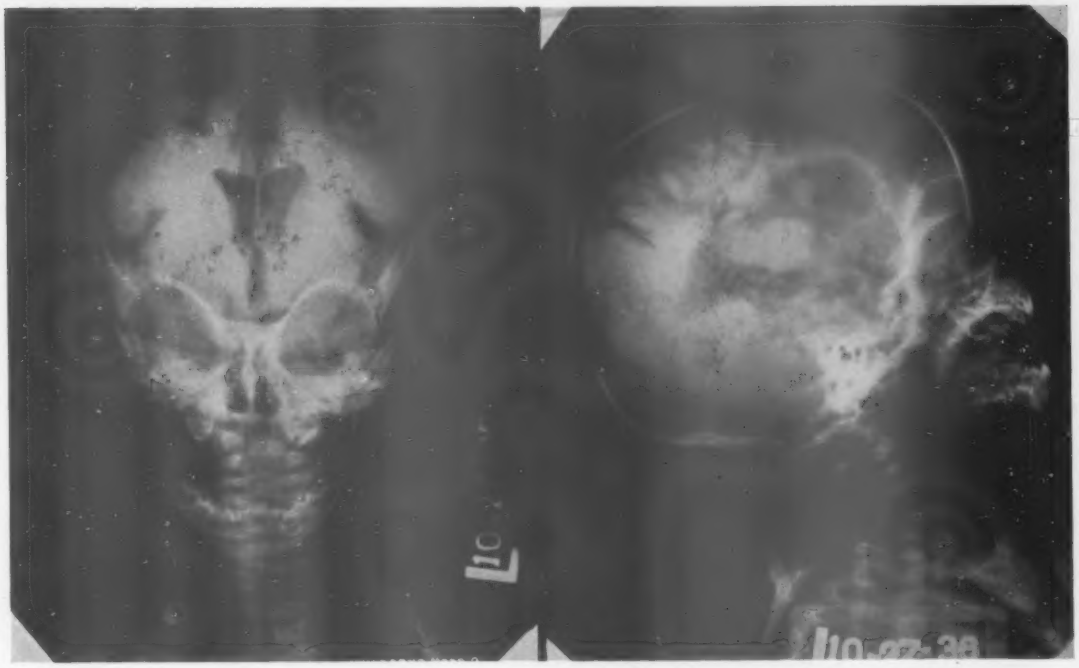

Fig. 3. Encephalograms at six months of age. The lateral and third ventricles are considerably enlarged. There is some air in the subdural space. The subarachnoid space is increased and the air extends deeply into the sulci which are markedly widened, indicating a decrease in the size of the cerebral gyri. The amount of brain tissue appears small in relation to the size of the cranial vault.

The patient was discharged from the hospital after completion of the first course of mapharsen and has subsequently been treated in the syphilis clinic of the Out Patient Department. The change to acetarsone was made because the parents found it impossible to bring the child to the syphilis clinic at weekly intervals.

The patient was readmitted at the age of six months for encephalography and cerebrospinal fluid study. The encephalograms showed dilated lateral and third ventricles and deep wide cortical sulci. The gyri appeared small (Fig. 3).

Examination of the cerebrospinal fluid at this time showed the following:

| | |
|---|---|
| Initial pressure | 90 mm. water |
| Appearance | Clear |
| Cells | 0 |
| Total protein | 34 mg. per cent |
| Sugar | 30 mg. per cent |
| Wassermann reaction | Positive |
| Colloidal gold test | Not done |
| Blood Hinton | Positive |

The development sequence of the patient has been as follows:

| | |
|---|---|
| 5 months of age | Sat alone |
| 10 months of age | First teeth—2 lower incisors |
| 11 months of age | Stood with support |
| 13 months of age | Walked |
| 17 months of age | Talked |

At the age of eighteen months a slight limp of the right leg was noticed, although the child otherwise appeared to be normal (Fig. 2). This limp was unimproved after three months' observation and the patient was again admitted for study at the age of twenty-one months.

A psychometric examination showed the mental development to be comparable to that of an eighteen months normal infant. There was a mild right hemiplegia. A muscle examination showed no paralysis, but the right leg was slightly weaker than the left, and the right arm was not used as freely or with as definite direction as the left. All of the functions were good. The right side of the face did not seem to be controlled as well as the left side.

Encephalograms showed the lateral ventricles to be still dilated to about the same degree, but there was an apparent marked increase in the amount of cortical tissue present as compared with the previous encephalograms (Fig. 4).

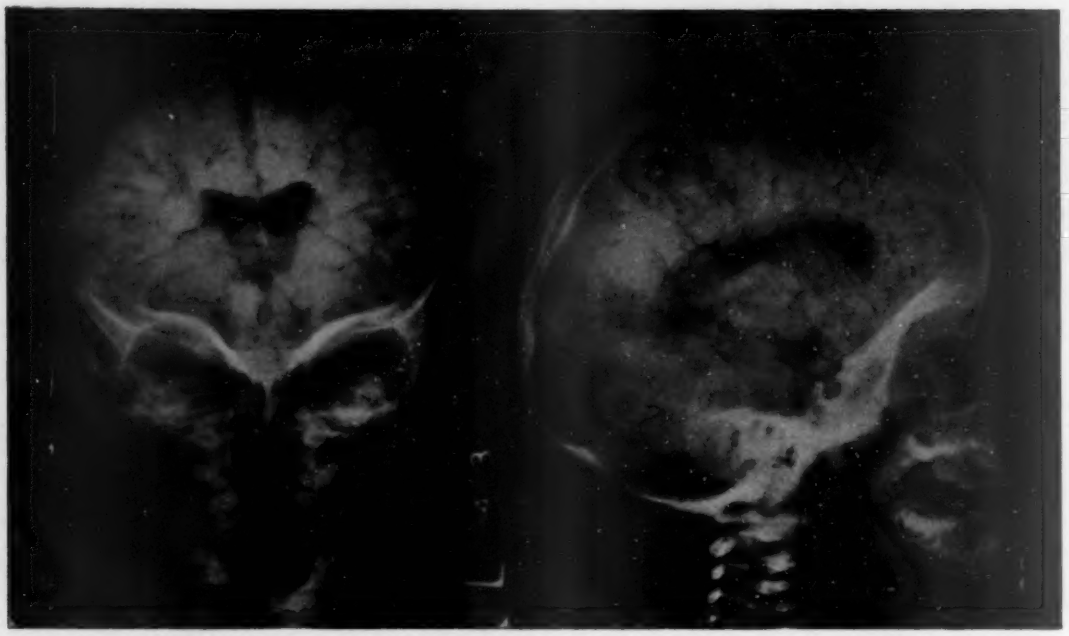

Fig. 4. Encephalograms at twenty-one months of age. The lateral and third ventricles are still large. The sulci, however, are of normal width and depth, and the amount of brain tissue appears to correspond to the size of the skull.

Examination of the cerebrospinal fluid at the third admission showed the following:

| | |
|---|---|
| Initial pressure | 100 mm. water |
| Appearance | Clear |
| Cells | 1 mononuclear |
| Total protein | 25 mg. per cent |
| Sugar | 33 mg. per cent |
| Wassermann reaction | Negative |
| Colloidal gold test | 0000000000 |

The blood Hinton test was still positive.

The patient was last seen at the age of twenty-five months and is still receiving continuous antisyphilitic therapy. Progression of her mental and physical development has continued and the limp is slowly improving.

## DISCUSSION

*Therapy*. The use of arsenicals early in the course of treatment of congenital neurosyphilis in young infants is considered dangerous because of the possibility of producing a severe reaction with a fatal outcome.[4] However, the use of intravenous arsenic in this infant was undoubtedly a life saving measure and the previous treatment may have prevented an untoward reaction to the arsenic. The use of maph-arsen was a new departure in that there was no record of its previous use in early, active, congenital neurosyphilis. Although the spinal fluid Wassermann was negative on the last admission, continuous intensive antisyphilitic therapy is still indicated for a considerable period of time.

*Encephalographic Findings*. The first examination at six months of age showed apparent deficiency of cortical tissue. A large part of the increase in the subarachnoid space may be explained by an increase in the amount of cerebrospinal fluid, but to the extent of our present knowledge the widening of the sulci can only be explained on the basis of a relative decrease in the size of the gyri. The normal width of the sulci on the second examination at twenty-one months of age would seem to indicate growth of the gyri which formerly appeared atrophic.

Several reports have been made on the subject of fixed cerebral defects in childhood and the value of encephalograms in prognosis.[1,2,5] The prognosis of hydrocephalus following congenital neurosyphilis is

generally considered poor.[4] A great deal of experimental work has been done on the subject of regeneration of central nervous system tissue, although there has been no conclusive proof that such regeneration can occur.[3,6] The unexpected change in this case is not presented as evidence of regeneration of brain tissue, but rather to indicate that the appearance of cortical atrophy as shown by encephalography in an infant may not necessarily carry a hopeless prognosis. The decrease in the size of the gyri on the first examination was possibly not due to irreparable damage, but to inhibition of brain growth by the infection. We have no valid encephalographic standards for young infants, and therefore no conclusive explanation for the changes in this case.

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# CALCIFICATION IN THE ARTERIES OF THE LEG

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FOR SOME time it has been our practice to make routine films of the arteries of the leg in certain of our cases without symptoms in the extremity, in an attempt to discover roentgen evidences of arterial change. In other cases calcification of the arteries has appeared as an incidental finding. During this same period we have

FIG. 1. Case A.W. Entire leg showing plaques.

roentgenographed a number of cases because of symptoms pointing to arterial disease of the legs. In the course of this work we have noted two distinct types of calcification of the arteries: small, irregular, densely calcified, discrete plaques, most marked in the upper third of the leg; and a diffuse, fine, net-like, even distribution of calcium involving usually all the larger arteries shown.

On reviewing the clinical records, we find that almost without exception the cases exhibiting the few scattered plaques are those with symptoms of arterial disease of the legs and absent or diminished pulsation in the foot arteries, while the cases with diffuse calcification have no complaints pointing to the arteries of the legs and no evidence of impaired circulation in the feet.

Table 1 shows the correlation between clinical and roentgen findings, and the illustrations show typical sections from several of our films. There are three apparent exceptions. M. Z. has been diagnosed sciatica on complaint of dull pain in left lower back and left leg which becomes cramping pain in cold weather and when he has a "cold." Examiner reports slight atrophy of left thigh and tenderness over left sacroiliac joint. The description of the

FIG. 2. Case W.H. Detail of leg showing plaques.

Table I

| Name | Age and Occupation | History and Physical Findings | Type of Calcification Date of Roentgenogram |
|---|---|---|---|
| W.H. | 53 Clerk | July, 1937, onset of intermittent claudication. Blood pressure 210/120. Feet cold; pulse not palpable | Plaques 9-28-37 |
| J.F. | 50 Owner candy store | 1933, pneumonia with myocardial disease. 1934, phlebitis left leg with edema; i.v. block by EKG. Intermittent claudication both legs. January, 1937, faint pulse both feet | Plaques 1-11-37 |
| B.A. | 55 Dress mfr. | 1933, coronary disease by EKG. Dorsalis pedis pulse not palpable, posterior tibials just felt; tingling in feet. Intermittent claudication | Plaques 4-9-36 |
| A.W. | 63 Retired | 1931, onset of intermittent claudication. 1934, impaired circulation in feet; pulse not palpable | Plaques 1-15-37 |
| I.R. | 49 Tailor | 1930, diabetes and arthritis. 1932, intermittent claudication. 1936, pulse still palpable in feet. 1937, "pins and needles" in toes | Plaques 2-10-37 |
| M.B. | 57 Tailor | 1935, myocardial change by EKG. Arteries tortuous and sclerotic but pulse palpable in feet. Intermittent claudication | Plaques 4-30-36 |
| G.W. | 49 Mgr. gas station | 1930, intermittent claudication; coronary disease by EKG. Pulse not palpable in feet | Plaques 5-19-36 |
| M.Z. | 55 Storekeeper | 1931, back injury in accident. Pain left lower back and leg, cramp-like in cold weather and with a "cold." Slight atrophy left thigh. Tenderness left sacroiliac. Diagnosed "sciatica" | Plaques 9-22-36 |
| M.H. | 59 Owner candy store | Onset of illness December, 1937, diagnosed coronary sclerosis. Pain in legs on walking | Plaques 4-5-38 |
| N.T. | 57 Manufacturer of ladies' coats | Dizziness in 1930; spells of loss of consciousness, possibly convulsions; angina pectoris past few years; intermittent claudication beginning in 1932; recent "glass boot" treatment for legs. Physical examination showed irregular pulse; heart large, sounds poor, systolic murmur at apex; pulse not palpable in feet | Few small plaques 6-9-38 |
| W.Z. | 51 Contractor | Coronary sclerosis April, 1937. Intermittent claudication in left leg. P.E.: left foot no pulse; right foot faint pulse dorsalis pedis, no pulse posterior tibial | Small plaques 9-20-38 |
| M.F. | 62 Store proprietor | Hypertension and myocarditis, 1933. "Acute fatigue" calves of legs with walking, limit 8 blocks; has to rest before going further. P.E.: hypertension, peripheral arteriosclerosis, tachycardia | Plaques 7-14-38 |
| M.M. | 57 Tobacconist | Diabetes 8 years. Since April, 1938, intermittent claudication both legs, becoming progressively worse; limit now 1 block. P.E.: no pulse felt in either foot | Plaques 11-14-38 |
| H.S. | 55 Cafe owner | 1934, intermittent claudication. 1935, anginal syndrome; EKG negative. Pulse not palpable in feet | Mixed 4-9-36 |

TABLE I—*Continued*

| Name | Age and Occupation | History and Physical Findings | Type of Calcification Date of Roentgenogram |
|---|---|---|---|
| L.L. | 60 Carpenter | August, 1937, cramping pains in legs on walking; limit now 1 block. P.E.: no pulse in right foot; slight pulse left foot, dorsalis pedis and posterior tibial | Mixed 5-31-38 |
| W.C. | 49 Clerk | Frequent colds and minor infections. Roentgenogram for trauma to foot | Diffuse 9-23-36 |
| A.F. | 57 Clerk | Underweight. Frequent colds. Arthritis in knees. Varicose veins both legs injected 8-3-37 | Diffuse 10-6-37 |
| S.R. | 69 Guard | Arthritis knee three weeks' duration | Diffuse 12-18-36 |
| A.B. | 55 Farmer | 1931, pyelitis (tuberculous?). Later pulmonary tuberculosis. Roentgenogram abdomen and pelvis | Diffuse 1-29-37 |
| J.L. | 57 Merchant | 1928, pulmonary tuberculosis. 1934, diabetes and multiple arthritis. 1935, stones removed from right kidney | Diffuse 7-24-36 |
| E.G. | 47 Chef | 1931, arthritis right knee. Pain right hip, thigh and calf diagnosed sciatica. Atrophy thigh and leg; crepitus right knee | Diffuse 3-15-34 |
| A.L. | 51 Actor | 1934, coronary sclerosis; pain lower back. Roentgenogram showed lumbar spondylitis | Diffuse 12-10-35 |
| E.N. | 40 C.P.A. | 1934, multiple arthritis. Loss of 50 lb. weight | Diffuse 10-20-37 |
| M.J. | 50 Salesman | 1933, automobile accident, fracture right knee | Diffuse 6-30-36 |
| B.S. | 52 Real estate | 1933, constant pain feet and legs, becoming cramp-like with walking. 1934, pulse in feet normal; no blanching. November, 1937, pulse in feet reported "fair" | Diffuse 11-20-34 |
| A.V. | 57 President wrecking company | 1931, diabetes; coronary disease. 1936, partial heart block by EKG. Pain in legs following exercise—not intermittent claudication. Pulse in left dorsalis pedis not felt, right normal. One examiner reports feet "warm," another "cold' | Diffuse 12-24-36 |
| H.F. | 59 Mgr. barber shop | Angina pectoris beginning 1932, increasing in severity. No leg symptoms | Diffuse 3-11-38 |
| M.E. | 60 Insurance agent | Cardiovascular disease and diabetes eventuating in cerebral embolism with right hemiplegia in March, 1934. Weakness right arm. Dorsalis pedis and posterior tibial pulses not palpable. Burning pains in left leg—not intermittent claudication | Diffuse with plaques 3-21-38 |
| N.F. | 66 Restaurant owner | History of coronary disease since 1930. Year ago redness and swelling in right foot with no pain or other symptoms. Physical examination negative—feet normal | Diffuse 6-15-38 |

Table I—*Continued*

| Name | Age and Occupation | History and Physical Findings | Type of Calcification Date of Roentgenogram |
|---|---|---|---|
| S.E. | 58 Manager plumbing supply Co. | Weakness, sweating, collapse July, 1938. Anginal pain since then. Numbness both feet, increased by walking. P.E.: heart slightly enlarged; varicose veins both legs; good pulse foot arteries, both sides | Diffuse 11-18-38 |
| A.J. | 61 Realtor | No leg symptoms. P.E.: organic mitral systolic murmur | Slight diffuse 10-3-38 |
| J.B. | 38 Sales executive | No leg symptoms. P.E.: dorsalis pedis pulse normal both sides | Sl ght diffuse 12-28-38 |
| E.W. | 41 Proprietor store | Hypertension several years, with attacks of dizziness, nausea and vomiting. No leg symptoms. P.E.: obesity, hypertension | Slight diffuse 9-20-38 |
| D.T. | 51 Silk mfr. | 1933, anginal pain recurring once or twice a week. Occasional pain in legs, not intermittent claudication. P.E.: hypertension, dorsalis pedis pulse palpable both sides | Slight diffuse 12-19-38 |
| M.K. | 43 Barber | Recurrent bacillary colitis since March, 1936. Fatigue, weakness, pain in ankles. P.E.: hypotension; arthritis both large toes, by x-ray | Diffuse 6-29-38 |
| N.M. | 50 Physician | August, 1937, precordial pain, fever, chill, followed by auricular fibrillation. No leg symptoms. P.E.: hypotension; good pulse dorsalis pedis and posterior tibial, both sides | Diffuse 10-19-38 |
| I.G. | 63 Contractor | Dyspnea and chest pain four years ago, increasing in severity. P.E.: overweight, hypertension, tachycardia, apical systolic murmur | Diffuse 11-21-38 |
| D.G. | 55 Genl. mgr. | 1937, diabetes, headaches, dizziness; precordial pain recently. P.E.: hypertension, tachycardia, normal pulse arteries of feet | Diffuse 7-15-38 |

leg symptoms is not as full as we would like and we have no information on the arterial pulse in the feet. It is quite possible that a more detailed study would bring out the picture of arterial disease which our films suggest. The description that we have of the case of B. S. is not typical of a true intermittent claudication, but it does seem to point to disease of the arteries of the leg. It is an exception about which we can draw no conclusions without more complete data. The pain of which A. V. complains "follows" exercise—the description does not suggest intermittent claudication and this term is not used in the history. The examiners' reports are conflicting. Most of these cases are disability claims which have been sent in from other cities and we are unable at this time to get further information on them.

We have made no attempt to differentiate between the several forms of disease of the arteries of the legs. We have simply considered two groups—one with symptoms and roentgen changes and a second without symptoms and with roentgen changes of a different type. None of these cases was examined by me, and in some the clinical material is not so comprehensive as we would like it to be in the light of our present interest. We have not as yet had opportunity to investigate the pathology of these two forms of calcification, but it would seem that, as a rule, the scattered,

FIG. 3. Case J.F. Detail of leg showing plaques.

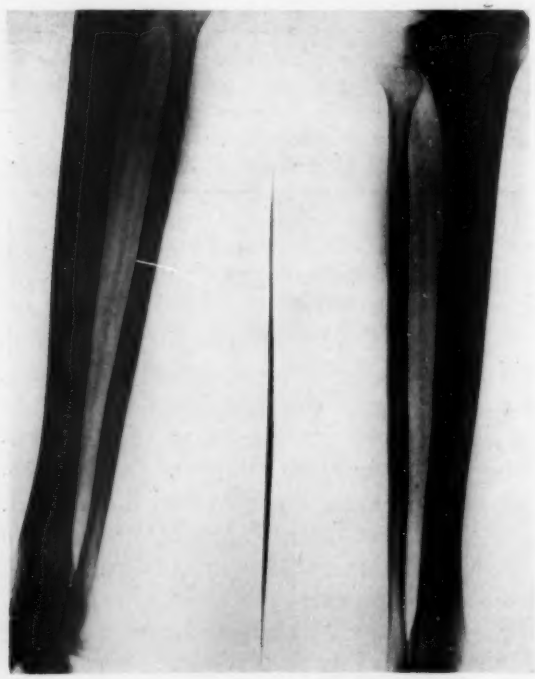

FIG. 4. Case A.F. Entire leg showing diffuse calcification.

discrete plaques are associated with encroachment on the lumen of the vessels, while the thin, diffuse, evenly distributed, general calcification is not accompanied by circulatory embarrassment.

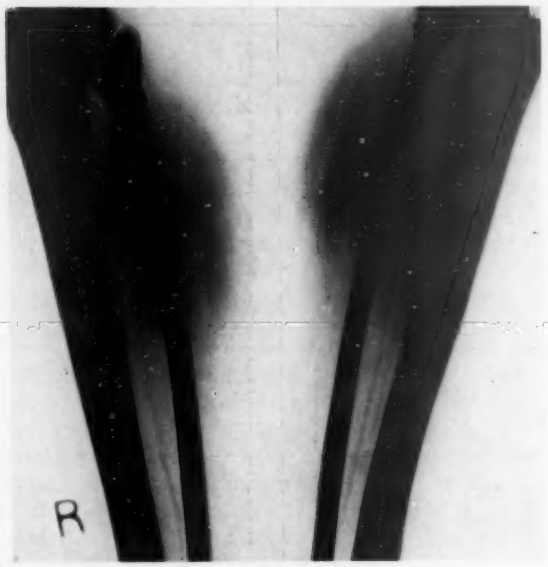


FIG. 5. Case A.V. Entire leg showing diffuse calcification.

FIG. 6. Case S.R. Knee showing diffuse calcification.

# ADENOCARCINOMA OF THE UTERINE FUNDUS*†

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THE present study concerns itself with the 104 patients with histologically verified carcinoma of the uterine fundus admitted to the University of California Hospital between 1916 and October, 1937. Eight cases in which this diagnosis was made clinically only are omitted from consideration. Sixty-two of the 104 patients were treated more than five years ago, and form the basis of all figures pertaining to cures. No patients have been lost from the follow-up.

The results obtained regarding such factors as age incidence, parity, family history and social status correspond with those which have been reported from many sources in the past, and require little comment.

## AGE

The average age of the 104 women was 57.1 years; of the 33 patients cured for five years, 53.4 years; of the 29 patients who did not survive for five years after treatment, 64.1 years. The age distribution by decades was as follows:

| | | |
|---|---|---|
| 20–29 years | 1 | |
| 30–39 years | 1 | |
| 40–49 years | 19 | |
| 50–59 years | 40 | 38.4% |
| 60–69 years | 35 | 33.6% |
| 70–79 years | 7 | |
| 80–89 years | 1 | |
| | 104 | |

The majority of the patients (72 per cent) were between fifty and sixty-nine years of age. Less than 2 per cent of the women were younger than forty years of age. It is not surprising that the women who died in less than five years after treatment were older than the women who were cured.

## PARITY

Twenty-seven and two-tenths per cent of the women had never borne children. Of the 72.8 per cent of the patients who gave a history of previous pregnancy, 7 had had abortions only. In agreement with the reports of others, we consider that the evidence is against childbearing as an etiologic factor in fundal carcinoma.

## FAMILY HISTORY

Twenty-four of the patients knew definitely of a cancer death among their more recent antecedents (23.3 per cent), while in 5 others there was a questionable positive family history. If we add the two together, at most 29, or 28.1 per cent, gave a positive family history of cancer, while 74, or 71.9 per cent, gave a negative history. One of the histories did not contain the requisite information. This percentage is probably not significantly different from that of any group of women in this age range. A control group of 600 patients between the ages of forty-five and seventy-five with non-malignant gynecologic conditions gave a positive family history of cancer in 28.6 per cent. While many of the patients knew little of their family's medical histories and thus the figures which have been obtained may be fallacious, still the evidence which is available does not support heredity as an etiologic factor.

## SOCIAL STATUS

A point of interest is that 45 (43.2 per cent) of these women were private patients in contrast to the large preponderance of clinic or charity patients making up the group with cervical cancer. While this is an old observation we are still at a loss to explain it. Presumably women who can

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afford private care, as a group, have been better cared for, better fed, and have worked less hard than any clinic patient group. Whether or not there is a possible relationship with etiology is an interesting speculation.

### SYMPTOMS

The most usual symptom was bleeding, which was either intermittent or constant. Sometimes the bleeding was preceded by, or associated with, a foul watery discharge; occasionally the latter was the only symptom. A small number complained of pain, but this was always a late symptom. Bleeding was usually not large in amount, and often was reported as *spotting* only. When the disease occurred before the menopause it was sometimes difficult to dissociate the bleeding from menstruation. A trifling number gave a history of menorrhagia only, and still a few others in the group past the menopause had had a menorrhagia preceding the cessation of menstruation. It was not possible to associate the development of the fundal cancer with a previous endometrial hyperplasia, as Novak and Yui have done in a number of their cases. The average duration of symptoms for all of the cases was 22.7 months. One patient had had intermittent bleeding for fifteen years, first starting two years after the menopause, yet she remained cured for over five years after radium and panhysterectomy. A second patient had had bleeding for seven years and a "weepy" discharge for five years; she too remained symptom-free for more than five years after treatment with radium alone. This patient finally died of cerebral hemorrhage, but at autopsy cancer was found in the abdomen. On the other hand, some of the patients with advanced growths had had symptoms for a few weeks only, and in a few others the disease was discovered accidentally. All in all, the symptoms were of long duration, yet cures resulted in many, suggesting that often fundal carcinoma is slow in its development and tends to remain local for long periods of time. The symptom post-menopausal bleeding is an important one, and frequently permits one to guess that the cause is a fundal carcinoma, even when other findings are not suggestive. The literature reveals that in 60–70 per cent of the cases, post-menopausal bleeding is due to genital malignancy. Therefore, this symptom should always be investigated by curettage if the cause is not obviously vaginal or cervical.

In the five year group, the average duration of symptoms for all of the patients was 26.8 months; for the cured patients 22.6 months; for those not cured 31.6 months. One would naturally expect a shorter duration of symptoms for the five year survivors than for the non-survivors. However, it should be pointed out that even 22.6 months is itself a long average duration of symptoms, and suggests that symptoms of long duration do not necessarily imply a poor prognosis.

### CLINICAL EXTENT OF THE DISEASE

There are *no* characteristic pelvic findings in cases of fundal carcinoma. The uterus is often enlarged slightly and softened, but slight enlargment does not necessarily mean that carcinoma is present, and usually a curettage must be performed in order to establish a definite diagnosis. Occasionally the uterus is not even palpably enlarged, and it is only the appearance of bleeding or discharge which brings the case under suspicion. Not infrequently fibroids are present in addition to the fundal carcinoma. This association is of great importance because of the diagnostic difficulties which their presence engenders. In this series fibroids were present in 18.1 per cent of the cases. In 7 of the 18 cases the fibroids so confused the picture that the diagnosis of carcinoma was not made until after curettage or hysterectomy. In the remainder, the diagnosis was either known or suspected. In a study of 229 cases of fundal carcinoma Norris and Dunne[14] reported the occurrence of associated myomas in 98. In 42 of these, the presence of cancer was unsuspected until

revealed by microscopic examination of the curettings. Ducuing and Guilhem[5] found 30 coincident corporeal adenocarcinomas in 580 cases of fibroids. In general, reports indicate the presence of fibroids in about one-quarter of the cases of carcinoma of the fundus uteri, and the presence of fundal carcinoma in 1 to 2 per cent of cases of fibroids. The questionable etiologic relationship, the masking of symptoms, the possibility of mistaken or deferred diagnosis, and thus incorrect therapy make the association one of great interest.

An analysis of the cases from the point of view of correctness of diagnosis is of interest. In 57 cases the diagnosis was either definite or strongly suspected because of the combination of postmenopausal bleeding or discharge and an enlarged uterus. Of course, confirmation was not obtained in many of these until a curettage had been performed, or the uterus removed. In 25 cases a diagnosis was not possible on the basis of the pelvic findings, the uterus being essentially normal in size, but the diagnosis was suspected on the basis of the history, and confirmed by curettage. In 20 cases the diagnosis of fundal carcinoma was not made preoperatively; in some of these, as mentioned previously, fibroids confused the picture, in others the lesion appeared to be cervical, and in still others the diagnosis was menopausal menorrhagia. In 2 cases not enough information was available in the histories to judge.

In order to test the value of the clinical findings in determining prognosis the cases were divided into five groups and a correlation with the eventual results attempted (Table 1).

TABLE I

| | All Cases | | Five Year Cases | | |
|---|---|---|---|---|---|
| | No. | Per cent | Cured | Uncured | Total |
| Uterus normal size or slightly enlarged. Movable. Definite diagnosis by curettage | 56 | 56.5 | 21 | 9 | 30 |
| Uterus enlarged and definitely fixed; or metastases present. Inoperable | 20 | 20.2 | 7 | 8 | 15 |
| Uterus enlarged by fibroids | 18 | 18.1 | 3 | 7 | 10 |
| Diagnosis made incidentally or accidentally | 2 | 2.0 | 1 | 1 | 2 |
| Recurrent cancer in cervical stump; with metastases | 3 | 3.0 | | | |
| Total | 99* | | 32 | 25 | 57* |

* In 5 cases no examination was recorded.

Although some of the patients in whom the disease seemed to be confined to the uterus on pelvic examination did not survive for five years, the majority did survive (21 of 30). About one-half of those who were considered inoperable remained cured, and one-half did not survive. These results show that a cure can generally be expected when the uterus is comparatively small and movable. This is a much more efficient indication of prognosis than we had expected to find.

Poor results were obtained in the cases complicated by the presence of fibroids, only 3 of the 10 patients having survived longer than five years. The explanation for this is not clear, unless perhaps deferred diagnosis was responsible for treatment only late in the disease.

### TREATMENT AND RESULTS

The treatment in this clinic, as in most others, has consisted of panhysterectomy for those cases in which the growth seemed confined to the uterus and the general condition of the patient made her a good surgical risk, and combined radium and roentgen therapy for the remainder. In a number of the patients radium was employed, and later followed by panhysterectomy. In a few cases a subtotal hysterectomy was performed; this occurred in cases in which the diagnosis was not suspected, and in those in which local conditions made panhysterectomy extremely difficult or dangerous. For the last seven years all patients have received high voltage roentgen therapy following the radium or surgery.

Up to five years ago, 38.7 per cent of the cases were treated radiologically only as compared with 59.5 per cent since that time. Whether this difference is due to increasing conservatism or to fewer early cases in the last five years is impossible to say.

Analysis of the results in the 62 five year cases reveals that 33, or 53.2 per cent, of the patients were still alive after five years. Table II contains the details for this group as well as for the later cases.

Thirty-seven of the 62 five year patients were operated upon, of which 24, or 64.8 per cent, survived for five years. Eighteen of the 37 patients operated upon were treated with radium preoperatively. The results with irradiation alone were not nearly so good, only 37.5 per cent of the patients having survived for the five year period. However, reliable comparison of the two methods of treatment is not possible as irradiation was reserved for those cases in which the growth seemed to be inoperable, or the general condition of the patient contraindicated operation. Indeed there are very few figures in the literature which reflect the relative merits of irradiation and surgery, because all of those reporting have treated their patients in the same manner as we have. Arneson collected a series of 473 operable cases reported by several different authors, in which irradiation alone had been used. Two hundred and fifty, or 53 per cent, of these women lived for five years.

Of the 33 patients in our series who lived for five years after treatment 7 have died subsequently of cancer, 5 with a recurrence

TABLE II

TREATMENT AND RESULTS

| | | Five Year Group 62 Cases | | | Cases Treated Less than 5 Years Ago—42 Cases | Total |
|---|---|---|---|---|---|---|
| Treatment | Cases | Dead | Alive | Survivals Per cent | Cases | |
| Panhysterectomy alone | 13 | 4 | 9 | 69.2 | 10 | 23 |
| Panhysterectomy plus radium | 18 | 6 | 12 | 66.6 | 3 | 21 |
| Supravaginal hysterectomy | 6 | 3 | 3 | 50.0 | 1 | 7 |
| Irradiation alone | 24 | 15 | 9 | 37.5 | 24 | 48 |
| Miscellaneous | 1 | 1 exploratory | | | 4 recurrent | 5 |
| | 62 | 29 | 33 | 53.2 | 42 | 104 |

of the original growth, 1 with cancer of the breast and 1 with cancer of the colon. Thus, survival for five years by no means assures one of complete cure. Furthermore, of those still living some may yet die of cancer. The occurrence of death from cancer after five years is being noted more and more frequently for all forms of genital cancer—as follow-up studies have become more complete and extended. Of the 5 women dying of recurrence after five years 3 were treated by irradiation alone and 2 by combined panhysterectomy and radium. Of the 15 patients who were treated radiologically and died in less than five years, 13 died of cancer and 2 of intercurrent disease. Of the 13 patients who were treated surgically and died in less than five years, 7 died of cancer, 4 of intercurrent disease and 2 from the operation itself. No operative deaths have occurred in the last five years, therefore the operative mortality for the 51 cases so treated is 3.9 per cent, not an excessively high figure.

So far this series contains an insufficient number of five year cases in which high voltage roentgen therapy was used to allow evaluation of its merits. As most authors do, we feel that panhysterectomy should be performed whenever possible, but that it is not necessarily a calamity if treatment has to be confined to a combination of radium and roentgen irradiation. Whether or not preoperative radium treatment is advantageous in cases suitable for surgery remains an unsettled question.

In Table III are listed the results obtained by others. These figures have all been reported since 1930, and should be quite representative of what can be accomplished by modern methods of treatment. It will be noted that a total of 3,480 cases has been collected; 1,641 of the patients survived for at least five years after treatment, a survival rate of 47.1 per cent. Until earlier diagnoses are made, or unless some improvement in treatment is developed, it seems unlikely that the present methods

TABLE III

RESULTS REPORTED BY OTHER AUTHORS

| Author | Operation | | | Irradiation | | | Irradiation and Operation | | | Totals | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cases | Alive 5 yr. | Per cent | Cases | Alive 5 yr. | Per cent | Cases | Alive 5 yr. | Per cent | Cases | Alive 5 yr. | Per cent |
| Burnam,[4] 1931 | 7 | 3 | 50 | 82 | 21 | 25.6 | 9 | 5 | 45.5 | 97 | 29 | 29.9 |
| Masson,[10] 1934 | 331 | 193 | 58.3 | 161 | 32 | 19.8 | 150 | 87 | 58 | 642 | 312 | 48.6 |
| Norris,[13] 1934 | 5 | 3 | 60 | 28 | 15 | 53.5 | 15 | 10 | 66.6 | 49 | 28 | 57.1 |
| Healy,[6] 1934 | | | | 18 | 18 | 100 | 29 | 22 | 75.9 | 47 | 40 | 85 |
| Newell and Crossen,[12] 1935 | 20 | 13 | 65 | 13 | 2 | 15.2 | 20 | 14 | 60.8 | 56 | 29 | 51.7 |
| Beattie,[2] 1933 | 12 | 9 | 75 | 15 | 3 | 18 | 8 | 2 | 25 | 35 | 14 | 40 |
| Norris and Dunne,[14] 1936 | 115 | 55 | 47.8 | 89 | 39 | 43.8 | | | | 211 | 94 | 44.5 |
| Healy,[7] 1936 | | | | | | | | | | 217 | 78 | 35.9 |
| Arneson,[1] 1936 | 20 | 13 | 65 | 18 | 5 | 28 | 10 | 9 | 90 | 48 | 27 | 56.2 |
| Collection of Arneson 1936 | 927 | 530 | 57 | 998 | 372 | 37 | 91 | 55 | 60 | 2016 | 957 | 47.4 |
| | | | | (Operable cases) | | | | | | | | |
| | | | | 473 | 250 | 53 | | | | | | |
| | | | | (Inoperable cases) | | | | | | | | |
| | | | | 290 | 30 | 10 | | | | | | |
| Morton, 1937 (This series) | 13 | 9 | 69.2 | 24 | 9 | 37.5 | 18 | 12 | 66.6 | 62 | 33 | 53.2 |
| Total | 1334 | 773 | 57.8 | 1446 | 516 | 35.7 | 353 | 216 | 61.1 | 3480 | 1641 | 47.1 |

can possibly better 50 per cent cure. Heyman's new method of packing the uterine cavity with small capsules of radium may prove to be a major development in treatment if the promise of better results, which his two, three and four year results seem to indicate, is realized in five and ten year results.

### MICROSCOPIC PICTURE

There has been considerable discussion in the literature regarding the division of fundal carcinomas into several histologic groups depending upon the pattern and the degree of cellular differentiation. Attempts have been made to establish the value of such classifications in determining the proper form of treatment and the prognosis. In 1923 Mahle[9] reported 186 cases from the Mayo Clinic with reference to cell differentiation. The best results were obtained in those cases in which there was the greatest cell differentiation. In 1930, Healy and Cutler[8] reported 100 cases from the Memorial Hospital in New York in which the cases were divided into five groups based upon pattern and cellular differentiation according to Ewing's classification. These groups were designated as diffuse or papillary adenoma malignum, simple adenoma malignum, adenocarcinoma, diffuse anaplastic adenocarcinoma, and adeno-acanthoma, named in the order of descending differentiation and ascending malignancy. They found that almost half of the cases fell into the first two groups, and that the majority of the patients with such growths remained cured for five years. The results were progressively worse the more undifferentiated the growth was. Newell and Crossen[12] divided 56 cases in a similar manner and came to similar conclusions, as did Murphy[11] still more recently. Murphy, however, concluded that prognosis could not be based upon the microscopic picture alone, without reference to such important factors as the gross extent of the growth, the patient's general condition, and her reactionary powers to treatment.

Among the cases at this hospital there were 84 in which it was possible to study the histology of the growth. Such a study was not possible in 20 because the slides had been lost, or the tissue was too small in amount, or the cells had undergone too much degeneration to permit proper evaluation.

As brought out by Beattie[2] in his recent careful study of 50 cases, it is extremely difficult to make a dependable histologic classification. The appearance of the growth may vary in different portions so that unless numerous sections are available erroneous impressions may be derived. Yet often the only material available for a study is the small amount obtained at curettage, generally represented on one slide. The value of conclusions based upon such material is questionable. The predominant histologic picture of a growth may be quite different from that seen in a single section of curetted material. With these reservations in mind, I have attempted to classify our material. In many instances only a single section made from curetted material was available, and in others the growth had been irradiated preoperatively so that the effect of irradiation had to be considered in interpreting the microscopic picture.

I found it possible to divide the material from the 84 cases into three large groups and one small group, depending upon the degree of cell differentiation and the general pattern. I have based the division as much as possible upon the classification employed by Ewing, Healy and Cutler, Newell and Crossen, and Murphy.

*Adenoma Malignum.* The picture conforms to that described by the above mentioned authors. No attempt was made to subdivide this group into papillary and simple forms, however. The epithelial cells are arranged on stalks of connective tissue, usually in a single layer. The cells are comparatively regular, and mitoses are infrequent. There is usually little or no invasion of the uterine muscle. The connective tissue stalks are usually thin and filmy. This is the most highly differentiated form of fundal carcinoma.

*Adenocarcinoma.* In this group, the picture is that of a conventional adenocarcinoma. The cells are arranged in alveoli, and are often piled up in several layers. Often there is penetration of the basement membrane, as well as invasion of the uterine muscle. The individual cells show a great deal more variation in size, shape and staining qualities than do those of the adenoma malignum. Mitoses may be frequent. These growths definitely present a less differentiated appearance than do those of the previous group.

*Medullary (Anaplastic) Adenocarcinoma.* Proceeding in the order of decreasing differentiation, growths classified under this heading show a diffuse, anaplastic, cell picture. There is little or no trace of alveolar arrangement. The individual cells may vary widely in appearance, giant forms and various other degenerative manifestations are common. Mitoses are frequent. There is usually marked invasion of the uterine musculature.

*Adeno-acanthoma.* Growths classified in this group show more or less transformation of the usual columnar cells into cells which resemble squamous epithelium. The transitions are usually abrupt. Sometimes the process is so extensive that it is difficult to find columnar cells. Whether this represents a true metaplasia or epidermization or is due to the development of heterotropic collections of squamous anlage is not definitely known. In any event the microscopic appearance is very striking.

Table IV

| | All Cases | | Five Year Cases | |
|---|---|---|---|---|
| | Cases | Per cent | Cases | Per cent |
| Adenoma malignum | 29 | 34.5 | 14 | 33.3 |
| Adenocarcinoma | 37 | 44.2 | 19 | 45.2 |
| Medullary adenocarcinoma | 13 | 15.4 | 6 | 14.3 |
| Adeno-acanthoma | 5 | 5.9 | 3 | 7.1 |

The number and percentage of cases classified in each of these four histologic groups are presented in Table IV.

While each group described seems quite characteristic, examination of the reports in the literature reveals considerable disagreement as to the proportions of all cases which the individual types constitute. Table V contains the percentage incidence

Table V

| | Mahle | Arneson | Bowing and Fricke | | Healy and Cutler | Newell and Crossen | Murphy | Morton |
|---|---|---|---|---|---|---|---|---|
| | Per cent | Per cent | Per cent | | Per cent | Per cent | Per cent | Per cent |
| Grade I<br>Grade II | 66.7 | 45.8 | 57.5 | Adenoma malignum I<br>Adenoma malignum II | 44.9 | 33.9 | 43.10 | 34.5 |
| Grade III | 29.0 | 37.5 | 22.5 | Adenocarcinoma | 42.5 | 48.2 | 48.20 | 44.2 |
| Grade IV | 4.3 | 16.6 | 20.0 | Anaplastic adenocarcinoma | 13.1 | 17.9 | 0.76 | 15.4 |
| | | | | Adeno-acanthoma | | | 0.01 | 5.9 |
| Number of cases | 186 | 48 | 40 | | 91 | 56 | 197 | 84 |

of the various histologic types reported by various authors and illustrates this disagreement clearly. It may not be possible to translate the classification employed by Mahle, Arneson, and Bowing and Fricke[3] into terms of Ewing's classification. Healy thinks that they correspond roughly as indicated in the table. The disparity in the figures inescapably throws considerable doubt upon the validity of such divisions.

TABLE VI

ANALYSIS OF RESULTS IN 42 FIVE YEAR CASES IN WHICH HISTOLOGIC CLASSIFICATION WAS POSSIBLE

| Histologic Variety | Number of Cases | Operation | | | Irradiation | | | Cure Per cent |
|---|---|---|---|---|---|---|---|---|
| | | Cases | Alive | Dead | Cases | Alive | Dead | |
| Adenoma malignum | 14 | 9 | 9 | 2 | 5 | 3 | 2 | 71.4 |
| Adenocarcinoma | 19 | 10 | 5 | 5 | 9 | 5 | 4 | 52.6 |
| Medullary adenocarcinoma | 6 | 4 | 3 | 1 | 2 | 0 | 2 | 50.0 |
| Adeno-acanthoma | 3 | 2 | 1 | 1 | 1 | 0 | 1 | 33.3 |
| Total | 42 | 25 | 16 | 9 | 17 | 8 | 9 | |

However, different fundal carcinomata *do* present different histologic appearances, and without doubt a rough grouping can be made. Such divisions should be kept as simple as possible, and should represent definite variations, otherwise the confusion becomes hopeless and the results cannot be analyzed by anyone except the original author.

Prevailing opinion (*vide supra*) indicates that better results are obtainable the more highly differentiated the growth. Our results seem to bear out this contention.

Unfortunately these figures are based upon a small number of cases, therefore I hesitate to draw conclusions from them. Moreover, the questionable soundness of such histologic divisions discussed above casts still further doubt on the value of such analyses in determination of prognosis. However, the adenoma malignum form seems definitely to be less malignant than the others and therefore such a finding can be translated into terms of a relatively good prognosis. I agree with Murphy that prognosis determination should not be attempted without reference to such factors as the age and general condition of the patient, her reactionary powers to treatment, and especially the gross extent of the growth. For instance, in this series 21 of 30 patients with enlarged or only slightly enlarged uteri survived for five years, and 71 per cent of patients with growths histologically of the adenoma malignum type survived for five years. Patients who have both an unenlarged uterus and an adenoma malignum obviously should have a relatively good prognosis. It is illogical, however, to consider the prognosis good just because the growth is histologically an adenoma malignum, if the growth has extended beyond the uterus. It is equally illogical to consider the prognosis poor just because the growth presents a medullary pattern if it is clearly confined to the uterus. In my opinion, prognosis cannot be based upon the single factor, histologic type, and attempts to do so should be considered illogical.

## CONCLUSIONS

1. Fundal carcinoma is typically a disease of the post-menopausal age. The

average age in this series was 57.1 years. Seventy-two per cent of the patients were between fifty and sixty-nine years of age.

2. Childbearing is not related to fundal carcinoma. Twenty-seven per cent of the women in this series had never been pregnant.

3. Spotty bleeding is the most common symptom. The average duration of symptoms is long, 22.7 months in the 104 cases reported. Symptoms of long duration often do not mean incurability.

4. There are no characteristic pelvic findings, but some enlargement of the uterus is usually present. When the uterus is only slightly enlarged and movable the prognosis is relatively good. Fibroids confuse the picture in about one-fifth of the cases. The results are poor in this group.

5. Panhysterectomy, when possible, has been the favorite method of treatment, and seemingly has given the best results. With present methods it is possible to cure about one-half of all patients presenting themselves with this disease.

6. It is possible to divide fundal carcinomas into several histologic groups based upon the degree of cellular differentiation and the general pattern. There are many sources of error in such divisions, however. Adenoma malignum forms seem definitely more benign than the others. Prognosis should not be based upon the single factor of histologic type.*

* For discussion see page 816.

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# EXPERIENCE WITH RADIATION THERAPY ALONE IN CARCINOMA OF THE CORPUS UTERI*

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DURING the fifteen year period from 1918 to 1932, 292 cases of carcinoma of the corpus uteri were admitted to the gynecological service at the Memorial Hospital. Of these, 109 were treated by a combination of irradiation and surgery, 9 by surgery alone, 65 were cases in which carcinoma was recurrent after operation elsewhere, 10 had received previous irradiation, 3 were too advanced for any active therapy, and 96 which had received no previous treatment were treated by irradiation alone. It is this group of 96 treated by irradiation only which constitutes the subject material for this review.

All of these cases were proved histologically to be carcinoma. Irradiation was chosen as the method of treatment in most cases because the patients were poor surgical risks due to advanced age, obesity, or intercurrent disease and would not stand irradiation followed by complete hysterectomy, or because operation was refused. These cases have been followed for five years or more, or until death. Seven cases in which the cause of death is not definitely known are grouped, in the statistics which follow, with deaths from carcinoma.

An attempt has been made to classify the cases both clinically and histologically and to correlate these classifications with end-results. The relation of extent of disease at first examination, and of type and duration of symptoms to survival has been investigated. The age incidence of carcinoma of the corpus in this series, and the relation of corpus carcinoma to the menopause and to child bearing will be mentioned briefly. The technique and results of treatment will be presented.

The age of the patients in this group of 96 varied from nineteen to seventy-nine years. Only 6 were under fifty, 13 were over seventy. The five year period of highest incidence was sixty to sixty-five, whereas the average age incidence of corpus carcinoma is about fifty-five years.

Seventy-eight of the patients were married or widowed, 18 single; 54 had borne children, 32 had not, and in 10 cases parity was not recorded; 21 gave a history of miscarriage, 65 did not and in 10 this fact was not mentioned in the patient's history.

Symptoms began after the menopause in 88 of the 96 patients. In 8 menstruation had not yet ceased. The average age at which menopause occurred was fifty years.

The principal symptom was recurrence of uterine bleeding after the menopause, or bleeding between periods if the patient was still menstruating. It occurred in every case but one in this series. This bleeding was usually slight and intermittent at first, tending to become constant and profuse as time went on. In many cases vaginal discharge white, yellow, or brown in color, and often of foul odor, accompanied or preceded the bleeding. Pain, usually localized in the pelvis and lower abdomen, occurred in 32 per cent of the cases and was a significant symptom in that 87 per cent of the individuals complaining of pain at time of first examination died of carcinoma, whereas only 43 per cent of these cases showed palpable extension of disease beyond the uterus when first seen.

Only 2 patients presented themselves for treatment because of symptoms of less than one month's duration; in 36 the duration was six months or less, and in 49, or one-half of the total number, symptoms had been present for from one to five years before the patients sought medical advice. As might be expected, the percentage of

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advanced cases was higher among those who delayed and the survival rate less.

The correlation of clinical grouping with results of treatment proved to be of considerable interest. The cases were placed in three clinical groups according to the gross size of the uterus and palpable extent of disease at first examination. Group I included those cases in which there was no palpable enlargement of the uterus and no evidence of extension of disease beyond it. Cases were placed in Group II when the uterus was slightly, moderately, or markedly enlarged but still freely movable and without evidence of carcinoma elsewhere. Cases fell into Group III when there was indication of extension beyond the uterus as evidenced by fixation of the uterus in the pelvis, palpable masses in the parametria or adnexa, vaginal metastases, or distant metastases.

There were 24 cases in Group I. Since the total number of cases in the series is close to 100 this figure also indicates the approximate percentage of cases in the entire group which were in this subdivision. Of these 24 cases, 46 per cent have remained free of disease for five or more years.

There were 47 cases in Group II. These were divided into smaller groups according to the extent of enlargement of the uterus. The five year results for slight enlargement and enlargement to size of six weeks, two months, and two and a half months gestation were approximately the same. The average was 47 per cent five year cure for all cases having an enlarged freely movable uterus not greater in size than a two and one-half months gestation. It is interesting and also very significant that not one of the 7 remaining cases in Group II was cured for five years or survived for five years. The uterus in each of these 7 cases was larger than a two and one-half months gestation, being estimated at three, four or five months in size. It is very likely that this increased size of the uterus may have contributed directly to the poor clinical result by preventing adequate approximation and dosage of radium to all parts of the tumor.

Since the amount of radiation per unit area varies inversely as the square of the distance from the source of radiation, it can be seen readily that a large uterus does not receive the same amount of radiation to all parts of its body, from radon capsules lying in the uterine cavity, as does a small uterus. For example, it has been calculated that 3,600 millicurie-hours from two radon capsules in a uterine cavity delivers approximately 7 threshold erythema doses at 1.5 cm., 1 T.E.D. at 5 cm., and ½ T.E.D. at 10 cm. from the radon capsules. Thus it is obvious that a dose which is adequate for a small uterus is totally inadequate for a large one. If the total dose is raised to compensate for this deficiency, necrosis is apt to occur in the uterine wall adjacent to the radium. With external roentgen irradiation alone by means of 200 kv., we are not at present able to deliver sufficient depth dose to cure corpus carcinoma. One must realize, therefore, that with present technique, at least, radiation therapy may not be adequate to control bulky corpus carcinoma and should be supplemented whenever possible by complete hysterectomy. Repeated treatments, not over 1,500 mc-hr. each, with three or four capsules may be the best procedure in large uteri, when one is compelled to rely on radiation alone. In such cases it is understood that roentgen radiation should also be used if possible.

In Group III there were 25 cases. In all of these there was palpable evidence of carcinoma beyond the uterus as evidenced by fixation of the uterus, parametrial or adnexal masses, vaginal or distant metastases. In this group there was only one five year cure. This case had a uterus which was only slightly enlarged but was classified Group III because of a metastatic nodule in the vaginal wall. Not only was there only one cure in Group III but 72 per cent of the cases died in less than one year after treatment and only 12 per cent lived more than two years.

TABLE I

CARCINOMA OF CORPUS UTERI
RESULTS OF RADIATION THERAPY ALONE

| Clinical Group | No. of Cases | Five Year Survival | Free of Disease 5 years or more | Death Due to Cancer | | | Death from Other Causes in Less than 5 yr. |
|---|---|---|---|---|---|---|---|
| | | | | Less than 1 yr. | 1–2 yr. | 2–4 yr. | |
| Clinical Group I, uterus not enlarged | 24 | 58% | 46% | 17% | 17% | 0 | 8% |
| Clinical Group II, uterus not larger than 2½ months gestation | 40 | 55% | 47% | 0 | 15% | 25% | 5% |
| Clinical Group IIA, uterus larger than 2½ months gestation | 7 | 0 | 0 | 29% | 43% | 28% | 0 |
| Clinical Group III, extension of cancer beyond uterus | 25 | 4% | 4% | 72% | 16% | 8% | 0 |
| All cases | 96 | 39% | 32% | 25% | 18% | 14% | 4% |

The extremely low percentage of cure and poor palliation from irradiation in Group III lesions is very discouraging because no other method of treatment can be offered the patient.

In order to discover the relation of histologic type of lesion to end-results, the 96 cases in this series were classified as indicated in Table II. There were 46 cases on which the pathologist's report was adenoma malignum or adenoma malignum Grade 2. In this group there were 30 per cent five year cures, 29 cases proved to be adenocarcinoma or adenocarcinoma Grade 2. Of these 31 per cent were free of disease for five or more years. There were 16 cases in which the pathologic diagnosis was adenocarcinoma Grade 3, one adenocarcinoma Grade 4, and one embryonal adenocarcinoma occurring in a young woman, aged nineteen. These are grouped together and the results for the group show 28 per cent five year cures, the young woman just mentioned being among them. There were 3 cases of adeno-acanthoma. Two of these have been free of disease for five or more years. These data indicate that the histologic type and grade of lesion does not strikingly influence the outcome from radiation therapy, and it seems to be of considerably less importance as a prognostic sign than the palpable extent of disease. The fact that the five year cure rate does not drop significantly with radiation therapy as the grade of malignancy increases is one of importance, since in treatment by surgery alone the higher grade lesions tend to do badly.

We now come to a consideration of the technique of treatment employed in this series of cases. Most significant are the cases in which treatment effected a cure. Of the 31 cases which have been free of disease for five years or more, 17, or 55 per cent, were treated by radium alone, and 14, or 45 per cent, by a combination of radium and roentgen radiation.

Intrauterine irradiation was given by means of a tandem or string of two or three radon capsules filtered by 0.5 mm. of platinum or gold and encased in a small rubber tube, the wall of which was 2 mm. thick. Strength of the radon varied from 80 to 200 mc. The capsules were inserted into

the uterine cavity under general anesthesia after gradual dilatation of the cervix and at the time the diagnostic curettage was done. They were sutured in place with a catgut suture passed through the cervix and tied in a bow knot so that it could be easily removed. The vagina was then packed snugly with gauze and a Pezzer catheter placed in the bladder. Patients were kept in bed until the radium was removed and for three or four days thereafter. The roentgen treatment in almost every case consisted of high voltage therapy (150–200 kv.) delivered at 50 cm. target-skin distance through a filter of 0.5 mm. of copper to four pelvic portals averaging 10×12 cm. in size. The average dose was 750 r per portal, treating each portal once, one portal daily. Since this amount of external radiation delivers only about 1 threshold erythema dose throughout the pelvis and since it has been estimated that from 5 to 10 threshold erythemas are necessary for control of corpus carcinoma, it was probably the intrauterine irradiation which was chiefly responsible for cure. A review of the dosage of radon employed in the cases which were cured reveals that 5 cases received 4,000 mc-hr. in a single dose or in two divided doses within two months, 9 cases received 36,000 mc-hr., 10 cases 3,000 mc-hr., 3 cases 2,500 mc-hr., 2 cases 2,000 mc-hr., 1 an adeno-acanthoma, 1,500 mc-hr., and 1, a cellular embryonal adenocarcinoma, 1,200 mc-hr. Experience, both in this clinic and in others, indicates that for the average uterus from 3,000 to 4,000 mc-hr. should be used if cure is to be expected.

We believe it is advisable in all patients, not too obese, or too feeble, or too elderly, to combine the use of deep roentgen therapy with the intrauterine application of radium.

Cases of carcinoma of the corpus at Memorial Hospital are now receiving 3,600 mc-hr. of radon within the uterus, a pelvic cycle of 200 kv. roentgen rays, 750 r to each of four or six portals at 70 cm., 0.5 mm. copper filtration, 30 ma. Complete hysterectomy is done six to ten weeks after irradiation is completed unless definitely contraindicated.

Since we are unable to palpate or visualize the disease in the corpus, it must be realized that we have but one way of controlling the adequacy of our treatment and that is by means of exploratory curettage

Table II

CARCINOMA OF CORPUS UTERI
RELATION OF HISTOLOGIC TYPE TO END-RESULTS

| Histologic Type | No. of Cases | Five Year Survival | Free of Disease 5 yr. or More (5 yr. cure) | Death Due to Cancer | | | Death from Other Causes in Less than 5 yr. |
|---|---|---|---|---|---|---|---|
| | | | | Less than 1 yr. | 1–2 yr. | 2–4 yr. | |
| Adenoma malignum Grades 1 and 2 | 46 | 39% | 30% | 11% | 24% | 22% | 4% |
| Adenocarcinoma, Adenocarcinoma Grade 2 | 29 | 41% | 31% | 31% | 17% | 10% | 0 |
| Adenocarcinoma Grades 3 and 4 Embryonal adenocarcinoma | 18 | 28% | 28% | 45% | 11% | 5% | 11% |
| Adeno-acanthoma | 3 | 66% | 66% | 34% | 0 | 0 | 0 |
| All types | 96 | 39% | 32% | 14% | 18% | 25% | 4% |

at some time following the radiation therapy. Our experience from a review of specimens removed by hysterectomy indicates that in at least 1 out of 3 cases there will be residual carcinoma six or eight weeks after radiation treatment. For this reason if a patient continues to show a uterine discharge three to six months or at any later time following irradiation, we believe exploratory curettage is essential, as in all probability carcinoma is still present in the uterus and if so further irradiation must be given.

A second treatment under such conditions should be limited to intracavitary use of radium, the dosage not to exceed 2,500 mc-hr. with an applicator made up of two or three capsules.

Complications from radiation treatment have been very few. Two cases developed hematuria and dysuria. One had a radiation ulcer in the bladder which healed after bladder irrigations and instillation of argyrol. The other on cystoscopy was found to have some injection and telangiectasis of the bladder base but no evidence of ulcer. Symptoms cleared up after bladder irrigations and argyrol. A third case developed frequency. Cystoscopy was negative and symptoms shortly subsided. One patient had transitory proctitis after insertion of radon seeds in a metastatic nodule in the vagina. One patient developed pyometra a year after insertion of a radon tandem in the uterus for 3,000 mc-hr. There have been no fistulas of any sort.

The results of treatment in the entire group of 96 cases are (Table 1) 39 per cent five year survivals (with or without disease), 32 per cent five year cures (meaning cases free from all evidence of disease for a period of at least five years). Twenty-five per cent of all cases died within a year after treatment, 18 per cent died at one to two years, and 14 per cent between two and four years after treatment. Ward and Sackett have recently reported 59 cases treated by irradiation alone with a five year survival rate of 35.6 per cent. Norris in 1936 reported 89 cases treated by irradiation only, with a five year salvage of 43.8 per cent. Arneson has summarized the results in 998 cases of carcinoma of the corpus treated by irradiation alone and reported by 17 different clinics, and finds that the five year survival rate for this group of 998 cases is 37 per cent. He has also collected statistics on the surgical treatment of corpus cancer, operable cases, and finds that in 927 reported cases 57 per cent were living after five years. It should be remembered that the cases in Group III of our classification fall into an "inoperable" group and that these are the cases which cause marked lowering of the five year survival rate for irradiation alone. If only Group I and II, or in other words the "operable" cases as far as the lesion itself is concerned, are considered the five year survival rate in this series is 56.3 per cent, closely approximating that reported from surgery alone. At the present time irradiation combined with complete hysterectomy is the method of choice, we believe, and should be used whenever the patient is able to withstand operation. Ward and Sackett report that irradiation plus surgery has yielded 57.1 per cent five year survivals in 21 cases. Norris reports 66 per cent in 15 cases. Arneson in 91 cases collected from the literature found 60 per cent five year survivals and in 10 cases of his own 90 per cent. Healy in his last five year series (1931) had 8 cases treated by irradiation and hysterectomy. All of these, or 100 per cent, were alive and well at the end of five years.

## SUMMARY

1. This report deals with 96 cases of carcinoma of the corpus uteri treated by irradiation alone.

2. In the majority of the cases the treatment was restricted to irradiation because the patients were bad risks for major surgery.

3. Despite this fact, the five year survival rate for all cases was 39 per cent, and for the "operable" cases 56.3 per cent.

4. A clinical grouping for prognostic

purposes has been presented which we believe may be of practical value.

5. It is significant that 56.3 per cent of the cases in which the uterus was not larger than a two and one-half months gestation and in which there was no evidence of metastases at the first examination survived five years or more.

6. Under radiation therapy the degree of malignancy as determined histologically does not appear to be as important a factor in prognosis as it is when surgery alone is the method of treatment.

7. Radiation therapy offers a valuable form of treatment, adequate for cure in many cases of carcinoma of the corpus in which hysterectomy cannot be utilized.

8. Pain due to carcinoma of the corpus before treatment is instituted would appear to be an important prognostic factor; 87 per cent of such cases in this series died of carcinoma.*

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* For discussion see page 816.

# SECONDARY FILTERS IN RADIUM THERAPY*

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RADIUM and radon, when used for gamma-ray therapy, are enclosed in sufficient metallic filter to remove all the primary beta rays. However, the gamma rays set up secondary beta radiation in the material of the filter itself, so that there is inevitably radiation of this type leaving the surface of the metal container. It is customary to cover the metal with a secondary filter designed to absorb this secondary radiation, whose own secondary radiation shall not be objectionable. This is usually rubber or some other organic substance; indeed recommendations for gamma-ray therapy usually include a secondary filter of about 2 mm. of rubber or its equivalent. On the other hand, data published from time to time have shown that, under certain conditions, the amount of secondary radiation measured from organic material or other substances of low atomic number may be of the same order of magnitude as that from heavy substances, and that a minimum is found for elements of intermediate atomic number. The amount of secondary radiation measured in any case depends not only on the material of the filter, but also on the geometrical relations between the source, filter, and measuring device (ionization chamber, biological material). It is always of very low penetrating power. Sievert and Benner[12] have calculated that 4–5 mm. of tissue will absorb 99 per cent of hard beta radiation; a considerably smaller thickness would suffice for the type of radiation under consideration.

It is important to consider the effect of this secondary radiation in therapy. If the difference in the amount effective in any given arrangement of radium and filter is significant, then the secondary filter should be selected accordingly. If it is not, the filter should be selected for convenience. In some cases the customary rubber may be satisfactory, in others a metal might be better. For instance, in applicators for intracavitary use, a metal container for the radium or radon tubes might facilitate both the preparation and the application. It is the purpose of the present study to investigate this matter.

Physical measurements of the intensity of the secondary radiation from different substances have been carried out by Bragg and Madsden, Kohlrausch and Schroedinger, and others; their findings have been collected and discussed at length by Sievert.[11] For the secondary radiation emerging on the side of the filter opposite the source of rays (that is, in the same direction as the primary beam), the so-called "emergence radiation," a decided minimum is found for elements of medium atomic number (between 25 and 50, which is the region containing copper, nickel, zinc, etc.). On the other hand, for secondary radiation emerging on the same side of the filter as the source, the "incidence radiation," the amount increases steadily with atomic number.

The possible importance of these facts in radium therapy appears to have been first pointed out by Sievert[11] in 1923. However, little attention seems to have been paid to this, no further reference being found to the subject until 1930. In that year Sievert and Benner[12] published further physical data along these lines, and almost simultaneously Piccard and Stahel[8] reported similar experiments. Benner[1] extended the work of Sievert, making more detailed studies with a larger number of secondary radiators, and using a magnet to eliminate the primary beta rays.

The first biological experiments on this

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problem were published about the same time, by Mottram.[7] Tumor fragments placed on mica (potassium aluminium orthosilicate ($KH_2Al_3(SiO_4)_3$), and on lead, were irradiated with equal doses from a radium plaque placed above the preparations, and were then implanted into rats. Many more takes were obtained with the fragments irradiated on mica than on lead. The secondary radiation acting here is, of course, the incidence radiation; the experiments do not appear to have been repeated for the emergence radiation.

Suetsugu and Braun[15] performed similar experiments with *Bacillus prodigiosus* and with *Ascaris* eggs, using both incidence and emergence secondary radiations. Their findings were qualitatively in agreement with those of physical experiments, a minimum emergence secondary radiation for a substance of medium atomic number (copper, as compared with wax and lead), and an incidence secondary radiation which increased steadily with atomic number.

Stahel[13] and his colleagues, Simon and Johner,[14] extended the physical measurements by determining the absorption of the emergence secondary radiation in cellophane. For each metal (aluminium, copper, lead) comparison was made with the secondary radiation from celluloid, reversible filters being used, metal on one side and celluloid on the other. The absorption in the aluminium foil of the chamber (0.005 mm.) was considered negligible. The secondary radiation from the aluminium was found to be 93 per cent that from celluloid, that from copper 77 per cent of the celluloid, and that from lead 126 per cent of the celluloid. After the addition to the metallic filters of cellophane filters equivalent to 1 mm. of water, the ratios relative to celluloid were aluminium, 96; copper, 92; lead, 93. After 4 mm. of water equivalent the radiations were practically equal (ratios 1.00, 0.99, and 0.98 respectively).

Since this secondary radiation is so unpenetrating, most of it being absorbed in the first millimeter of tissue, any effect in the therapeutic application of the rays must be very superficial. The skin erythema is probably the result of changes occurring in the first 2 mm. of tissue, or less, hence variations in this reaction might be expected to result from the use of different filters. Stahel, Simon, and Johner[14] attempted to observe such differences. They used a circular wax moulage 2 cm. thick, with a distribution of radium tubes which gave a uniform intensity over an 11 cm. circle. On the lower surface of the moulage, which would be in contact with the skin, one quadrant was left bare, and the other three covered with thin foils of aluminium, copper, and lead. The moulage was applied over the external surface of the thigh for a dose calculated to produce a mild erythema and light pigmentation. Only six tests were made and no definite difference was observed in any of them. These investigators also tested both the emergence and incidence radiation in its effect on *Drosophila* eggs, obtaining qualitative agreement with the results of the physical experiments. Tests on the eyes of rabbits were inconclusive.

Benner and Snellman[2] performed a series of experiments to test the difference between ordinary platinum needles and needles with an outer shell of palladium (atomic number 46). All the needles used had equal composite filters of palladium and platinum; in six of them the platinum was outside and in the other six, palladium. Only six experiments were made on the human skin, different groupings of the needles and different times of exposure being used. In all cases the needles were fixed directly to the skin, and the exposure was sufficient to produce a sharp reaction. In all cases the reaction under those with platinum outside appeared first; in three these remained stronger, while in the other three the end-results were the same. Similar tests were conducted on the ears of rabbits, and similar results obtained. Attempts were made to compare the reaction in interstitial application, but the formation of a necrotic zone around the implant, probably due to a mechanical effect on the

tissue, made this impossible. In the histological sections the necrotic zone was about 1 mm. thick; it would not be probable that significant amounts of secondary radiation would penetrate to a greater distance.

In the experiments mentioned above, little or no attempt has been made to correlate quantitatively physical and biological findings, or, indeed, to perform the physical measurements in such a way as to render them applicable to quantitative correlation. For this purpose it is necessary to have the size, shape, and material of the ionization chamber such that all the secondary radiation effective in the biological experiment is registered, and no other. Hence different physical set-ups are necessary for measuring radiation from tubes and from flat applicators; the size and shape of the applicator in any case may also be significant.

The present report is concerned with the development of a method to measure correctly the radiation from tubular sources, comparable with those which may be used in intracavitary or interstitial therapy, and to correlate these measurements with skin tests made with the same tubular sources. The secondary radiators used were catalin (effective atomic number about 6), aluminium (13), copper (29), and gold (79).

## IONIZATION MEASUREMENTS

One of the ionization chambers is shown schematically in Figure 1 (actual size). The inner tube, containing the radium, is of platinum 0.5 mm. thick. This fits snugly into either (1) a catalin* tube surrounded by one of the metals, or (2) a tube of one of the metals surrounded by catalin.† The thickness of the metal is always 0.5 mm., that of the catalin, 1.5 mm.,‡ the outside diameter of the combination 6.30–6.43 mm. depending on the particular tube used. The outer surface of this composite tube forms the inner electrode of the ionization chamber, the catalin one being coated with India ink to make it conducting. Surrounding this tube is another of lucite (an organic material similar to celluloid and catalin, but a much better electrical insulator), 3 mm. thick, held rigidly so that there is a fixed and definite spacing between the two. This outer tube is coated with India ink on its *inner* surface; near its center two scratches are made in this coating, 7 mm. apart and completely around the tube. The region between the two scratches is thus insulated electrically from the rest of the inner surface, and forms the collecting electrode of the chamber;

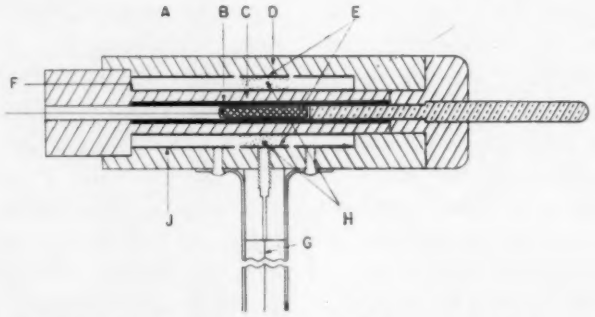


FIG. 1. Diagram of ionization chamber (actual size). *A*, radium tube; *B*, metal sleeve; *C*, catalin sleeve. Alternately the catalin is in position *B* and the metal in position *C*. Whichever is at *C* is the charged electrode. *D*, outer lucite sleeve; *E*, collecting electrode; *F*, lead to 22½ volt battery; *G*, lead to measuring instrument; *H*, ionized volume; *J*, guard ring.

* Catalin is a celluloid-like substance, whose composition is given by its manufacturers as 64 per cent carbon, 19 per cent oxygen, 5 per cent hydrogen, 9 per cent moisture, 2 per cent ash, the metal in the ash being sodium. It was used instead of celluloid because it is easier to machine.

† The metal tubes were prepared to specification by Baker and Company, who also lent the gold tubing for the experiment. The authors hereby express their appreciation for this courtesy.

‡ It may be asked why 1.5 mm. of organic material was selected instead of a greater thickness; it was because this is about the thickness of rubber tubing usually used as a secondary filter in intracavitary applicators.

the remainder of this surface functions as a guard ring. The inner electrode is charged to a potential of 22½ volts by means of batteries, this having been found sufficient to insure saturation. The collecting electrode is connected to the measuring instrument by means of a fine aluminium wire passing through the wall of the lucite tube as indicated.

The outer shell was mounted permanently in such a way that all the various inner tubes could be slipped into it in turn, and held in the proper position for centering. Thus the relative ionizations produced by the various filter combinations were measured in ionization chambers whose volumes depended on the spacing between the inner and outer tubes. In order to permit extrapolation to zero spacing, to obtain the value of the ionization directly at the surface of the source of secondary radiation, a series of outer tubes were made, providing spacings of approximately 2.8, 1.7, 1.2 and 0.6 mm. The actual spacing for every combination of shell and core was determined by measuring the capacity of the chamber as a concentric cylinder condenser. The capacity per centimeter of length is $1/2 \log_e(b/a)$, where $a$ and $b$ are the radii of the inner and outer conducting surfaces respectively. The diameter of the inner cylinder (removed from the apparatus) was measured with micrometer calipers. That of the outer, and hence the spacing, or the volume of the chamber, was readily calculated.

The source of radiation was a needle containing 9.8 mg. of radium. The active portion was 12–14 mm. long, the filter 0.5 mm. platinum.* This needle was inserted into the inner tube of the apparatus as indicated in the diagram.

The position of the radium relative to the collecting electrode longitudinally was determined by inserting it gradually, taking readings at various positions until a maximum was established. In this position it is to be assumed that correct centering has been obtained. As a matter of fact, the range for the maximum reading allowed a back and forth motion of about 2 mm. The middle of this range was selected for the setting, and a stop made so that the radium was always inserted to the same point.

The thickness of the lucite sleeve (3 mm.) was sufficient to produce equilibrium for the secondary radiation generated in it. The addition of more organic material outside it made no difference in the magnitude of the ionization current.

Ionization measurements were made with the Failla vacuum tube apparatus,[3] which permits making many readings in a short time, and which has been calibrated to give values of the ionization current in electrostatic units per second.

For every metal-catalin pair, values of the total emitted radiation (primary and secondary) were determined, for the four available spacings and for both positive and negative potential on the chamber. The average for the two potentials was taken as the correct reading in every case. (The differences were of the order of a few per cent. They are due to the difference between the number of electrons reaching and the number leaving the collecting electrode. This should not be confused with leakage or residual ionization in the chamber.) The electrostatic units per cubic centimeter were calculated for each particular volume.

The values thus obtained do not indicate directly the relative amounts of secondary radiation emitted from the faces of the inner electrodes, but include a difference due to the absorption of the primary gamma rays in the different substances. Since the metal tubes were 0.5 mm. thick, this is, particularly in the case of the gold, an appreciable factor. Its relative value for the three metals can be determined from the measurements made with the catalin inner electrode, with the small metal tubes directly over the radium needle. Taking the ionization from the catalin-aluminium pair as 100 per cent, the relative

* The authors desire to express their indebtedness to the Radium Chemical Company for the loan of this source.

TABLE I

RELATIVE ABSORPTION OF GAMMA RAYS

| Chamber | Aluminium | Copper | Gold |
|---|---|---|---|
| I (Largest) | 100 | 94.0 | 88.0 |
| II | 100 | 93.5 | 88.0 |
| III | 100 | 94.8 | 87.8 |
| IV | 100 | 94.3 | 88.0 |
| Average | 100 | 94.2 | 88.0 |

decrease due to copper and to gold can be calculated, with the results shown in Table I. In order to correct for this absorption of the primary radiation, the values for the ionization with the catalin-copper pair should be increased by 5.8 per cent, and those for the catalin-gold pair by 12 per cent. After this has been done, the variations among the resulting values are due to the differences in the secondary radiations.* The relations among them may best be shown by taking those for one substance as 100 per cent and calculating the others on this basis. The results thus obtained are shown in Table II, for the four chambers, related to the catalin radiation as 100 per cent. The values vary somewhat as the volume decreases, that is as the spacing between the electrodes becomes less. If a curve is plotted for each substance, and extended back to zero spacing, the values thus found should be those actually at the surface of the secondary radiator; they are given at the bottom of the table. The close agreement of these values with those of Stahel, reported above, may be significant, but may, in view of the differences in the type of ionization chamber and arrangement of source and filter, be accidental.

TABLE II

SECONDARY RADIATION EMITTED BY VARIOUS TUBULAR RADIUM CONTAINERS

| Chamber | Spacing mm. | Relative Intensities of Secondary Radiation | | | |
|---|---|---|---|---|---|
| | | Catalin | Aluminium | Copper | Gold |
| I | 2.9 | 100 | 89 | 75 | 105 |
| II | 1.7 | 100 | 90 | 76 | 107 |
| III | 1.3 | 100 | 90 | 77 | 109 |
| IV | 0.7 | 100 | 91 | 78 | 113 |
| Extrapolated | 0 | 100 | 92 | 79 | 119 |

* The ionization in the chamber is not entirely due to primary radiation and secondary radiation from the inner electrode, but contains also a contribution due to scattered and secondary radiation from the outer shell. In the present problem, however, this is of no consequence. For each chamber this contribution is effectively a constant factor, and the differences in the readings are, as stated, due to differences in secondary radiation from the inner electrode.

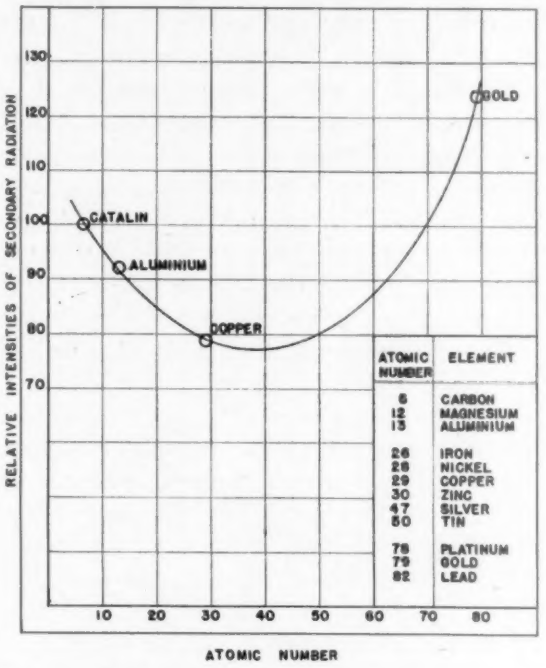


FIG. 2. Curve showing relation between atomic number of radiator and secondary radiation.

The relation between atomic number and secondary radiation, measured by the method described, is shown in Figure 2, where the experimental points are indicated by circles. The atomic numbers of certain other substances are shown in the inset table. It is apparent that any substance from iron to tin would be expected to emit secondary radiation of about the same intensity as copper, while those toward both extremes in atomic number would emit more.

It is of interest to find out how this secondary radiation would be absorbed in tissue. In order to make an approximation to this, sleeves of catalin 0.5 and 1 mm. in wall thickness were made, which fitted tightly over the metal or catalin inner electrodes of the ionization chambers. These, coated with India ink, now became the electrodes, and readings made with this arrangement gave the relative ionizations due to the secondary radiations after they had passed through 0.5 or 1 mm. of catalin. (In this arrangement the catalin may be considered as a satisfactory tissue substitute for a first approximation.) These sleeves could, of course, be used only with the two larger chambers, but the values obtained with these two agreed closely. The results are shown in Table III and in Figure 3.

TABLE III

RELATIVE SECONDARY RADIATION FROM VARIOUS TUBULAR RADIUM CONTAINERS AFTER PASSAGE THROUGH TISSUE-LIKE MATERIAL

| Radiator | Millimeters Catalin Absorber | | |
|---|---|---|---|
| | 0 | 0.5 | 1.1 |
| | Relative Secondary Radiations | | |
| Catalin | 100 | 100 | 100 |
| Aluminium | 90 | 97 | 94 |
| Copper | 76 | 89 | 93 |
| Gold | 107 | 93 | 94 |

Two phenomena are involved here, the absorption of the secondary radiation from the metal, and the addition of secondary radiation from the catalin sleeve. In the case of the gold, the first evidently preponderates in the beginning, while for the copper the second is more important throughout. For the aluminium the changing importance of the two probably accounts for the shape of the curve; it is not due to experimental error. After traversing about a millimeter of tissue substitute, the radiations from the surfaces of these tubular applicators are all reduced to within less than 7 per cent of each other.

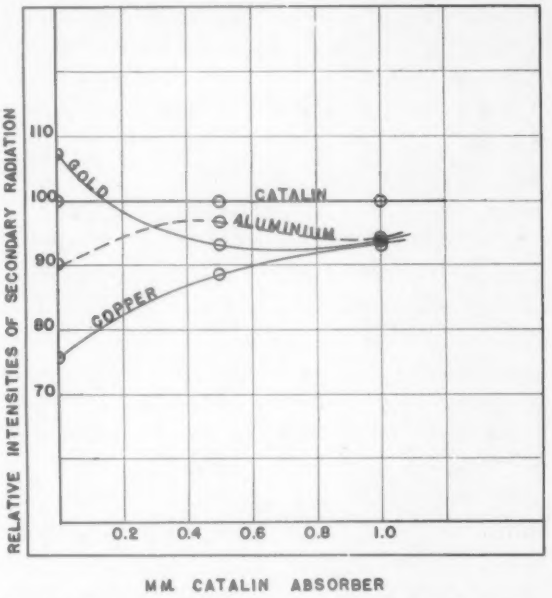


FIG. 3. Curve showing relative intensities of secondary radiations from certain substances after passage through tissue-like material (catalin).

SKIN ERYTHEMA TESTS

In order to compare ionization and erythema data, it is important that the irradiation in the two cases shall have been done under the proper conditions. Accordingly, the applicators for the skin tests were identical with the inner portion of the ionization chambers. That is, the source of radiation was in a 0.5 mm. tube of gold-platinum alloy, which was enclosed in the same catalin-metal or metal-catalin combinations as those used in the chambers. (The fact that radium was used in the ionization measurements and radon in the skin tests is of no significance.) The radiation at the surface of the applicator is that measured by extrapolation to the surface of the inner electrode of the ionization chamber. The presence of a considerable thickness of tissue instead of the 3 mm. outer shell of the chamber is of no importance, since adding material outside this outer shell produced no increase in ionization. In the final series of tests, as described below, the applicators were not simply placed upon the skin but were covered with several centimeters of tissue equivalent material, to agree more closely

both with the completely enclosing ionization chamber and with the actual conditions of therapy.

The skin tests were commenced before the ionization measurements had been made, therefore an allowance for the difference in gamma radiation transmitted by the different metals had to be made on the basis of information already available. Data previously published from this laboratory [4,9] indicated that from a gamma-ray beam previously filtered by 0.5 mm. of gold, 0.5 mm. aluminium would remove less than 1 per cent; of copper, about 3 per cent; and of gold, about 12 per cent. Accordingly it was decided, for the preliminary tests, to give the same dose with the aluminium and copper tubes, and to increase this by 12 per cent for the gold. When the data of part 1 of this paper became available, it was found that the allowance for the gold had been correct for the applicators in question; that which should have been made for the copper would not have been significant in the first series of tests, and was later taken care of.

It was felt that comparisons in degree of reaction could best be made if all reactions were visible but faint, hence a dose just above the threshold was desirable. Previous work with erythema tests indicated that with the primary filter of 0.5 mm. of gold, and the radon-skin distance of 3.15 mm., a mild but definite reaction should be expected with about 30 mc-hr. Radon tubes in the range of 25–35 mc. strength were always used, so that each treatment was administered in about an hour. The tubes were placed transversely either on the thigh or upper arm, always 6 cm. apart. The order of the tubes was varied from one individual to another, and was found, in summarizing the results, to have been without significance. Patients were observed daily for the first week, every few days for another two weeks, and then at longer intervals for about three months.

For the first series of tests, the doses were 30 mc-hr. for the aluminium and copper shells, and 34 mc-hr. for the gold. This dose generally produced a mild erythema, followed by tanning. In no case

TABLE IV

RESULTS OF SKIN TESTS COMPARING ALUMINIUM, COPPER, AND GOLD

| Case No. | 24 hours | 1 week | 1 month | Final |
|---|---|---|---|---|
| I | Au > Cu > Al | Au > Al > Cu | Al > Au > Cu | Au > Al = Cu |
| II | No visible reaction | Au = Al > Cu | Au = Al = Cu | Au > Al > Cu |
| III | Au only visible | Au > Cu > Al | Au > Cu > Al | Au = Al = Cu |
| IV | No visible reaction | Au > Al > Cu | Au = Al > Cu | Au > Cu > Al |
| V | Al only visible | Al > Au Cu missing | Au > Al > Cu | Au > Al > Cu |
| VI | | | | Au > Al > Cu |
| VII | No visible reaction | Au > Al Cu missing | Au > Al > Cu | Au > Al > Cu |
| VIII | No visible reaction | Au > Cu > Al | Au > Al > Cu | Au > Al > Cu |
| IX | Cu > Au Al missing | Cu > Au > Al | Au = Cu > Al | Au = Cu > Al |
| X | No visible reaction | Au > Cu > Al | Au = Cu > Al | Au = Cu > Al |

* The sign > denotes "is greater than."

TABLE V

RESULTS OF SKIN TESTS COMPARING CATALIN, ALUMINIUM, AND COPPER

| Case No. | 24 hours | 1 week | 1 month | Final |
|---|---|---|---|---|
| I | Cat > Al > Cu | Cat > Al > Cu | Cat > Al > Cu | Cat > Al > Cu |
| II | Cat = Al > Cu | Cat > Al > Cu | Cat > Al > Cu | Cat > Al > Cu |
| III | Cat = Cu > Al | Cat > Al > Cu | Cat > Al = Cu | Cat > Al > Cu |
| IV | Cat = Al Cu missing | Cat > Al > Cu | Cat > Al > Cu | Cat = Al > Cu |
| V | Cat = Al > Cu | Al > Cat > Cu | Al > Cat > Cu | Al > Cat > Cu |
| VI | Al only visible | Al = Cu Cat missing | Cu > Al > Cat | Cu > Al > Cat |

was there desquamation. Ten patients were irradiated; a synopsis of the observations is given in Table IV. It is evident that the final result produced by the gold was much more marked than the others, and that in general the aluminium produced a greater reaction than the copper.

Since the gold produced so definitely the most marked reaction, and since from a practical point of view it would not be desirable as the outer container in many intracavitary applicators, it was omitted from the next series, and an all-catalin tube substituted, this being of the same outer diameter, of course, as the metal ones. A series of 6 cases was done to compare catalin, aluminium, and copper; in this group all doses were the same, 30 mc-hr. The results are summarized in Table V. The copper still produces the least reaction; the catalin is somewhat more effective than the aluminium.

From the data thus far obtained, it appeared that the effect of the copper secondary radiation in producing skin reaction was less than that of any of the other materials tested. However, it is true that up to this time no correction had been made for the absorption of the gamma radiation in copper, which in the meantime had been found in the ionization measurements to be 6 per cent. Another point to be considered was that in practice rubber, rather than catalin or any similar plastic, is generally used for the container and secondary filter in intracavitary applicators. Accordingly a third series of tests was made, in which the total filter in all cases was equal, and in which the results of the radiation from copper, catalin, and rubber could be compared directly. The catalin and the rubber (of the same thickness, 1.5 mm.) were used over copper inner tubes having a 0.5 mm. wall, while the copper outer tube, also 0.5 mm. thick, was used as before, over a catalin tube of 1.5 mm. wall. Thus all the applicators had practically the same filtration and the same outer diameter. In this series of tests, also, it was considered advisable to place blocks of scattering material of a tissue substitute above the tubes, to approximate more closely the situation when the applicator is used in a body cavity, or interstitially. Accordingly, cubical blocks of pressd-wood, 6 cm. on a side, were prepared, each having a groove in one face to fit the tubular applicator. Their use is indicated in the diagram of Figure 4.

Under these conditions, 10 patients were tested. The dose was increased to 40 mc-hr. for every case, in order to have reactions a little more definite than those previously obtained, but still not severe. Reddening and bronzing occurred in all cases, but in only a few was there any desquamation. Photographs of some typical reactions are shown in Figure 5. The results obtained

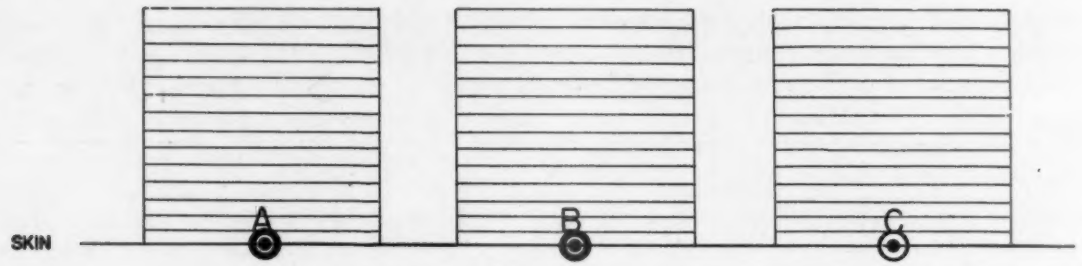


FIG. 4. Tubular applicators with pressdwood blocks, for skin tests. *A*, catalin over copper; *B*, rubber over copper; *C*, copper over catalin.

in this series are given in Table VI. Here, as in both the earlier series, the reaction produced by the copper is definitely the least. While in the previous tests there might be some suspicion that the absorption of primary gamma radiation in the copper, which was not allowed for, was responsible for this result, in this series this was definitely not the case. Between the catalin and the rubber the difference is not marked. This is to be expected, since both are organic mixtures.

## DISCUSSION AND CONCLUSIONS

Ionization and erythema measurements agree in demonstrating that the secondary radiation emitted from tubular radium sources, such as those used in the experiments here reported, is definitely less for copper than for substances of considerably higher or lower atomic number. According to ionization measurements, the secondary radiation from copper is approximately 25 per cent less than that from catalin. A quantitative estimate of the difference according to the biological reaction cannot be made directly. However, long experience in observing skin tests has resulted in the impression that it is not possible to detect definitely differences of less than 10 per cent in the dose administered. The present data demonstrate marked differences in the

TABLE VI

RESULTS OF SKIN TESTS COMPARING CATALIN, RUBBER, AND COPPER

| Case No. | 24 hours | 1 week | 1 month | Final |
|---|---|---|---|---|
| I | No visible reaction | Cat > Rub > Cu | Cu > Cat > Rub | |
| II | Cat > Cu Rubber missing | Cat > Cu > Rub | Cat > Rub > Cu | Cat > Rub > Cu |
| III | Cu > Cat > Rub | Cat > Rub > Cu | Cat > Rub = Cu | Cat > Rub = Cu |
| IV | Cat = Rub = Cu | Cat > Rub > Cu | Rub > Cat > Cu | Rub > Cat > Cu |
| V | Cu > Cat > Rub | Cat > Rub > Cu | Cat > Rub = Cu | Cat > Rub = Cu |
| VI | Cat > Rub > Cu | Cat = Cu > Rub | Cat = Rub = Cu | Cat > Rub > Cu |
| VII | Rub > Cat > Cu | Cat = Rub > Cu | Cat > Rub > Cu | Rub > Cat > Cu |
| VIII | Cat = Rub > Cu | Cat = Rub > Cu | Cat > Rub Cu missing | Rub = Cat > Cu |
| IX | Cat = Rub Cu missing | Rub > Cat > Cu | Rub > Cat Cu missing | |
| X | Rub > Cat > Cu | Rub = Cat = Cu | Cat > Cu > Rub | |

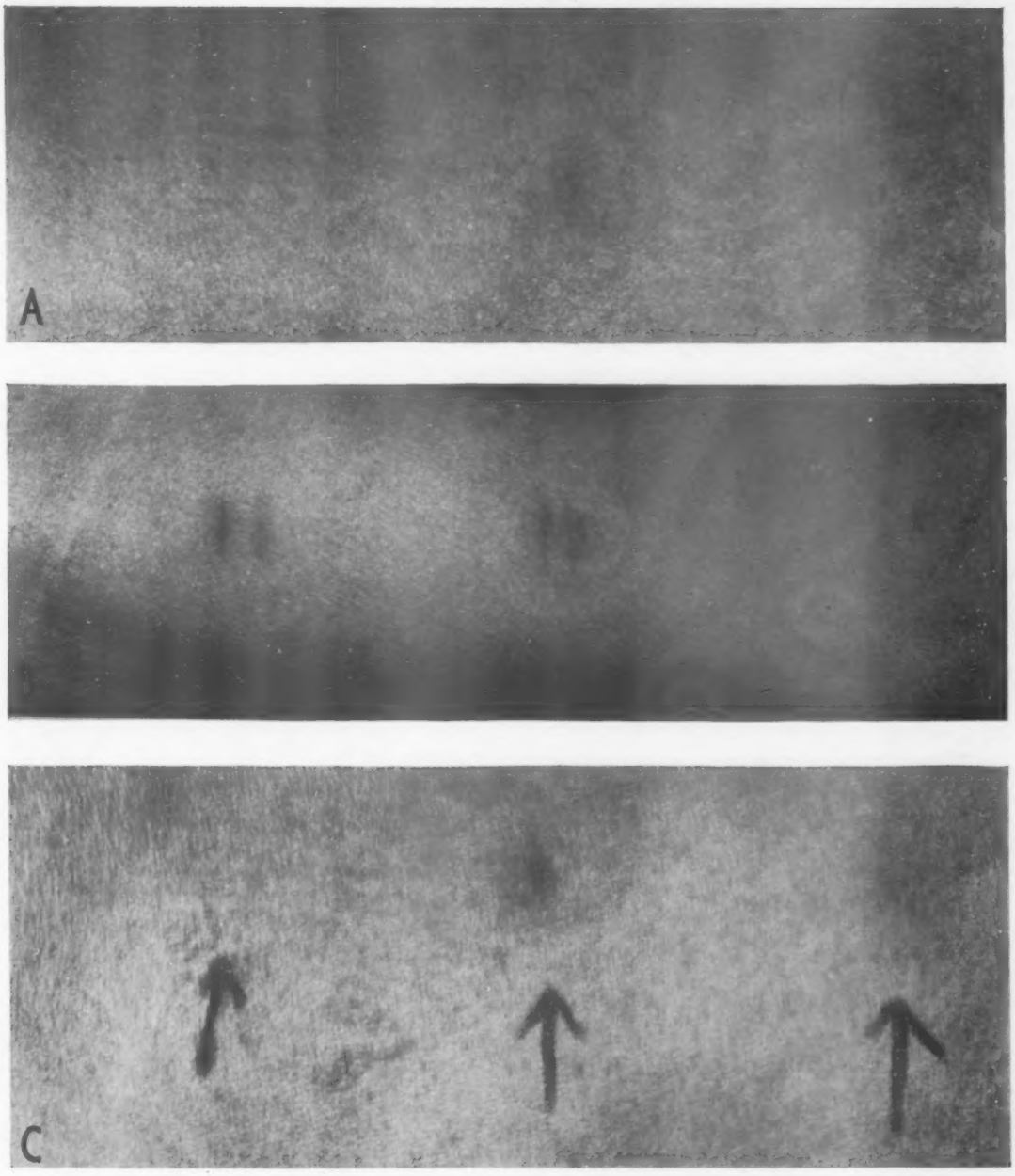


Fig. 5. Typical skin reactions. The secondary radiators from top to bottom are: *A*, copper, aluminium, catalin; seven weeks (Case iv, Table v); *B*, catalin, rubber, copper; six weeks (Case viii, Table vi); *C*, rubber, catalin, copper; five weeks (Case ii, Table vi).

reactions due to copper and to catalin, and probable differences between those for catalin and aluminium, and aluminium and copper. It is therefore permissible to deduce that there is probably a difference of at least 20 per cent between the effective radiation from copper and that from catalin. Rubber is apparently close to catalin in its effect, and there is no doubt that any metal close to copper in atomic number would also be close to it in secondary radiation.

On this basis it is evident that if a radium container for intracavitary applica-

tion had an outside shell of nickel, stainless steel, or some such substance, instead of rubber as ordinarily used, the secondary radiation effective at its surface would be of the order of 20 per cent less. The millicurie- or milligram-hour dose should be increased to allow for the absorption of the primary gamma radiation in the shell (6 per cent for 0.5 mm. Cu); there would then be no difference in the radiation delivered to distances of more than a few millimeters in the tissues, whereas there would be a decrease of about 20 per cent in the radiation effective at the surface.

The doses ordinarily used in intracavitary therapy are of the order of magnitude of many threshold erythema doses (3,000 mc-hr. from a cervix tandem gives approximately 100 threshold erythema doses at the surface of the applicator). It is evident that in such a case severe superficial reactions are bound to occur. A decrease of one-fifth in the radiation producing these reactions, with no loss to the deeper dose, should be highly desirable.

The experiments reported in the present paper were all performed with tubular applicators, and the conclusions drawn from them are not directly applicable to flat surface applicators such as plaques. However, the close agreement of the data here presented with those of Stahel and his colleagues, which were obtained with a flat ionization chamber, under conditions approximately applicable to external irradiation, makes it seem reasonable to extend these conclusions to such treatments.

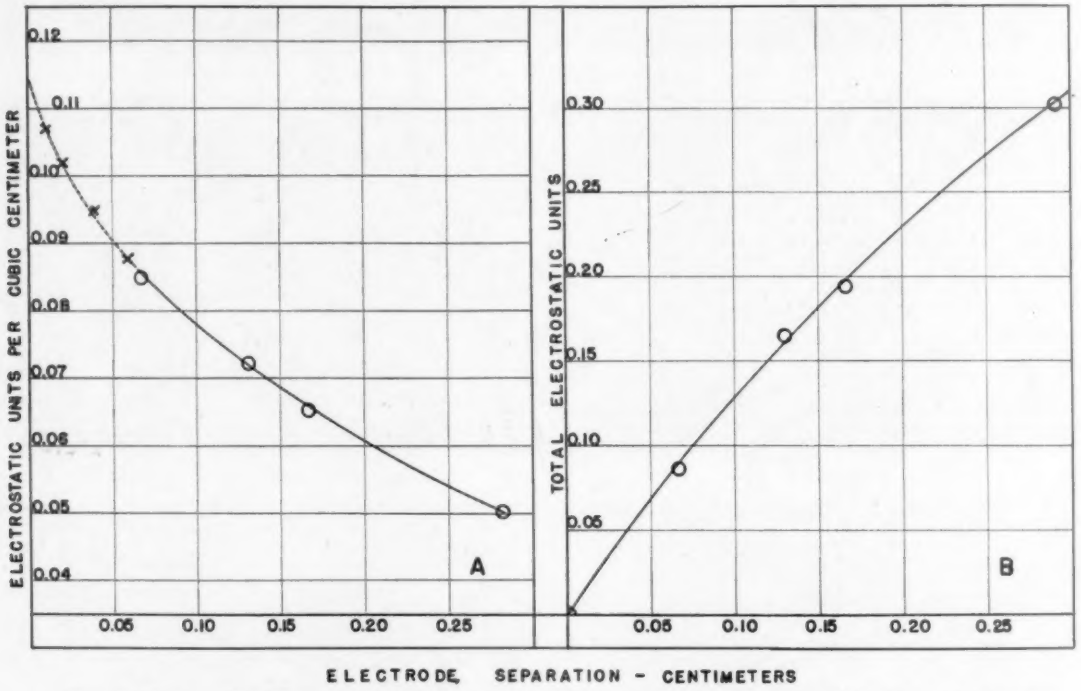


FIG. 6. Curves showing: *A*, variation in ionization per cubic centimeter with electrode spacing; *B*, variation in total ionization with electrode spacing.

The study of the absorption of the secondary radiation in catalin throws an interesting light on the region in which erythema and pigmentation are probably produced. It was found that after 1 mm. of catalin, all the materials tested gave secondary radiations varying by less than 10 per cent from each other in amount. This difference would not be definitely detected by the type of skin tests used. It would appear, therefore, that such reactions are either caused or profoundly influenced by changes occurring within the

first millimeter of tissue. Little information on this subject has been found in the literature. Failla, Twombly, and Marinelli[6] indicate that the erythema reaction for gamma rays probably occurs within 1 mm. of the skin surface; their study of the available literature supported this opinion. The present investigation confirms their conclusion.

The ionization data for the catalin tube affords an interesting confirmation of previously obtained values for the erythema dose from gamma rays expressed in "tissue roentgens."* For the calculation of this dose it is necessary to know the electrostatic units per cubic centimeter at the surface of the catalin tube, and to know the millicurie-hours required to produce a threshold erythema with the same tube. This latter amount has been found experimentally, according to the usual procedure,[10] to be 22 mc-hr. The value for the electrostatic units per cubic centimeter is found by the following procedure: In Figure 6*A* is given the curve for the value of electrostatic units per cubic centimeter with decreasing electrode spacing; the circles enclose the experimental points. Direct extrapolation of this curve to zero spacing might well lead to an uncertainty in the end-point of 20 per cent. However, it is possible to make this extrapolation satisfactorily by the following method. In Figure 6*B* is given the experimental curve for the total electrostatic units with decreasing electrode separation. Since there is no leakage or extraneous ionization, this curve must pass through zero for zero spacing. From this curve as drawn, therefore, it is legitimate to read the values for the total electrostatic units for spacings smaller than those used experimentally, and to calculate therefrom the electrostatic units per cubic centimeter. This process was carried out for the points indicated by crosses in Figure 6*A*, giving the broken part of the curve and the zero intersection at 0.114 e.s.u. per cc. This is the ionization due to 9.8 mg. in one second, at 760 mm. pressure and 20° C. temperature. With an 8 per cent correction to reduce to standard conditions, this amounts to

$$0.114 \times 1.08 \times 60 \times 60 \times \frac{22}{9.8} = 950$$

"tissue roentgens" for 22 mc-hr. Failla and Marinelli[5] have reported for a somewhat similar, but larger, applicator, 1,015 "tissue roentgens." The difference between the two is well within the range of experimental variation (10 per cent) always to be expected in erythema measurements.

* The "tissue roentgen" is that quantity of radiation which produces in the tissue, *at the point where it is utilized*, the same number of ions as does one roentgen under the conditions of its definition. It is necessary at present to differentiate between them, since the equilibrium conditions set up for the definition of the roentgen are not always realized in the tissue, particularly at the surface of the body.


## SUMMARY

The secondary radiation from tubular gamma-ray applicators of various materials has been studied by ionization measurements and by skin erythema tests. Results for the two series of experiments are strictly comparable because the ionization chamber used and the skin applicator were composed of identical units, so that the distribution of the radiation was the same in both cases.

The two series of experiments agree in demonstrating that the secondary radiation is considerably less for substances of intermediate atomic number than for those toward either end of the atomic scale.

It is concluded that intracavitary applicators should be enclosed in a substance of intermediate atomic number, such as stainless steel or nickel, rather than in rubber or celluloid.

A study of the absorption of the secondary radiation in catalin shows that differences practically disappear after the radiation has traversed about a millimeter of tissue-like substance. This indicates that skin erythema and pigmentation are the result of changes occurring in the first millimeter of tissue.

The value for the gamma-ray erythema dose, expressed in "tissue roentgens," derived from the experiments here reported

agrees with that previously reported from this institution, for a different applicator and ionization chamber.

In conclusion, the authors wish to acknowledge their indebtedness to Dr. G. Failla, who suggested this problem, for his assistance and interest throughout the course of the work.

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## DISCUSSION ON PAPERS OF DRS. MORTON, HEALY AND BROWN, AND QUIMBY, MARINELLI AND BLADY

DR. HENRY SCHMITZ, Chicago. The greatest difficulty in the intrauterine use of radium is that we never know where the radium tubes are. They may change position within the uterus with the change of position of the patient. About five years ago, I presented a paper at this Society on an improvement in technique in the therapy of carcinoma of the body of the uterus by using a Y-shaped applicator. A turn of the arm would separate the radium tubes and they could not change position. The dose of radium advised at that time was 6,000 mg-hr. Since then we have treated a great number and our clinical results do not differ from those given this morning. The group of beginning cases should be kept separate for the reason that we should endeavor to gain an idea as to whether in the early cases the results are better than in the advanced cases.

To determine the extent of the carcinoma inside the uterus we must use diagnostic curettage to ascertain whether the tissue is confined to the endometrium or whether it has invaded the myometrium, parametrium or adjacent organs and glands. The diagnosis of carcinoma should always be confirmed by biopsy. I am not able to give any statistics but I am under the impression that unless a case can be radically operated on by a surgeon it should be treated by irradiation.

DR. H. J. ULLMANN, Santa Barbara, Calif. I was glad to have the statement made twice that a prognosis regarding irradiation effect should not be based on the histologic grading of the tumor. We have all seen tumors histologically graded as radioresistant disappear rapidly under irradiation, and conversely, some supposedly radiosensitive regress only slowly or not at all. I should like to ask Dr. Healy if he has any data on the regression or disappearance of tumors based on the examination of uteri that have been removed after a thorough course of irradiation. I have one case in which no trace of malignancy was found in a uterus removed eight weeks after the irradiation. I use pre-radium roentgen irradiation for the same reason Dr. Healy gave for fractionating the radium dosage. I have seen patients that appeared to have considerable involvement at first examination show a 50 per cent regression

following external irradiation when re-examined prior to the first radium treatment. I believe this is due to a reduction of the inflammatory reaction about the tumor rather than a reduction in the tumor itself as the time is too short to expect such a marked regression except in lymphoid tumors.

I was particularly interested in Dr. Quimby's paper because I make my own applicators. I had been using aluminum for my secondary filter for about ten years and anyone who has worked with aluminum knows how difficult it is to thread properly, especially if the thread is fine and shallow. Then Dr. Lauritsen suggested that I use an intermediate weight metal, such as copper or stainless iron, and I changed from aluminum to monel metal which is much easier to work than aluminum and retains its polish. If rubber is used, either as tubes or in other forms, considerable handling is required in forming an applicator. When metallic applicators are used the radium capsules may be dropped into them with forceps, and with copper tubing the final applicator may be bent as needed to fit the uterine canal, also by the use of forceps. I have never found it necessary to suture my uterine applicators to the cervix because I have a series of rods of different lengths which may be bent. They are threaded at one end to fit the tube holding the radium, and have a disk at the other which is held against the cervix by the uterine packing. These permit the placing of the radium at any point in the canal desired, with a certainty of its remaining there.

I would like to ask Dr. Quimby if the statement regarding the heavier metals for secondary filters applies only to gamma radiation or if they can also be applied to the longer wave roentgen radiation.

Dr. Edwin C. Ernst, St. Louis, Mo. The foregoing papers have been indeed worth while, and since the several subjects presented were so thoroughly discussed by the respective essayists, there is relatively little that I might add except by way of emphasis.

The question of uterine malignancy continues to be less and less a treatment management problem from the irradiation and surgical standpoints. Therefore, it was gratifying that Drs. Morton and Healy were in such close agreement and both stressed that each corpus uteri type of malignant tumor should be considered an individual treatment problem, rather than showing preference for any one single method of therapy.

One phase of this subject was rather lightly touched upon, namely, the very early upper uterine canal malignancies simulating menorrhagia or fibroid tumor pathology. Many such cases are sent in for consultation and treatment by the physicians practicing in smaller communities, and invariably a routine curettage is insisted upon. Occasionally, such a desirable preliminary examination is refused, and the only remaining expedient is to administer approximately one-half the usual roentgen-ray dose to the ovaries. Prior to continuing and completing the total roentgen-ray dose, a careful vaginal examination will disclose improvement findings, otherwise an immediate curettage or operative procedure is insisted upon. In 11 such cases during the past fifteen years, small patches of beginning malignancy were discovered high in the uterine canal and all these cases survived the five year period following surgery and radiation therapy, except two.

In the more effective application of radium relating to the employment of greater dosages, Dr. Quimby has, as usual, stimulated our interest, and we sincerely hope that these researches may be continued.

Dr. Healy (closing). In answer to Dr. Ullmann's question as to the relative frequency with which cancer is found in the uterus six to eight weeks afterwards, in approximately 1 out of 3 cases we find residual disease. That is why we do not like to depend upon irradiation alone. If we are to depend upon it alone we should consider an investigative or diagnostic curettage three or four months after the primary treatment, because by that time presumably all worth while effect from the irradiation has terminated. I will not do it unless there is some indication for it, because many of our cases are cured by radiation therapy with only one treatment, but if there is a persistent discharge then it should be re-investigated. I would like to say that in about 88 per cent of these cases the patients have passed the menopause before uterine bleeding begins. In Dr. Morton's cases, only 2 were under forty years of age. We have only 4 under forty years of age in a series of 300.

Dr. Quimby (closing). I was glad Dr. Ullmann brought out the fact that in addition to

the possible advantage to the patient, there is a definite advantage to the operator in handling metal applicators instead of rubber ones. Certainly metal containers are easier to manipulate.

I was asked the thickness of the metal filter to be used. As I stated in my paper, all the experiments were made with 0.5 mm. secondary filters. At least this thickness would be necessary in practice, in order to be sure that the container would be strong enough to remain undamaged through the necessary manipulations: 1 mm. might be even more satisfactory. In that case, the correction in dose to allow for the gamma-ray absorption would have to be somewhat greater. If 0.5 mm. copper secondary filter is substituted for rubber, the millicurie-hour dose should be increased by about 6 per cent; for a 1 mm. filter, the increase should be about 10 per cent.

About secondary filters for roentgen rays: In this case the secondary radiation which is important is the characteristic roentgen radiation of the filter, instead of the secondary beta rays which are significant in gamma-ray therapy. The characteristic radiation from the ordinary copper filter (or the copper layer in the composite filter) is absorbed by the customary aluminum secondary filter; the characteristic radiation from the aluminum by a very few centimeters of air. Any secondary electrons which may be produced are of such low energy that they have no practical significance.

With regard to protection about the eyes and mouth: if shields are made to protect from roentgen rays it is possible to use enough lead to cut off the radiation entirely from the shielded regions; there is no need of using anything else. For gamma rays, it would be preferable to put a secondary filter of brass, stainless steel, or some such material, between the lead and the skin. However, in such treatments the actual difference in dose may not be so significant since the total dose is not so great as in intracavitary treatments.

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# TREATMENT OF METASTATIC CERVICAL LYMPH NODES*

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THE use of irradiation as the method of choice in the treatment of primary malignant lesions of the lip, mouth and throat is rapidly gaining favor, and many surgeons who have familiarized themselves with this type of therapy believe that the improved cosmetic results, lowered mortality and economic saving to the patient tend to place the more radical surgical procedures in a secondary position. However, the care of the neck is still a highly controversial subject and a study of the literature does little to clarify the situation. Extravagant claims are in many instances supported by very little reliable statistical evidence in articles dealing largely with technique.

Since the advent of the Coutard method it seems logical to divide metastatic nodes into two large groups: first, those produced by lesions in the pharynx, posterior third of the tongue and tonsillar area, and second, those produced by lesions on the face, lip, tongue, floor of the mouth, cheek and palate. The success of irradiation in eradicating the glands secondary to most throat lesions has completely removed the first group from the field of surgery. A perusal of Table 1, which covers a series of 12 of our own cases, shows that, although many of these patients died, the glandular metastases did not recur after one roentgen series had been administered. Unfortunately the care of the second group is an entirely different story.

Before proceeding further with the consideration of epidermoid carcinoma of the head and neck, it seems desirable to challenge a statement found repeatedly in the surgical literature to the effect that the chance of cure with irradiation methods becomes negligible after the primary lesion reaches a diameter of more than 1 cm. Not only do many of the large tumors of the face and lip respond well to efficient therapy but a surprisingly large number produce no metastatic nodes in the neck. Illustrative cases are shown in Figures 1 and 2. Although face and lip cancers are known to metastasize slowly, one is led to wonder whether the absence of the manipulation which, of necessity, accompanies radical surgery might not play a rôle in the freedom from cervical invasion in many of these patients.

For more than thirty years surgeons have proclaimed the radical block dissection of the neck as the only efficient form of treatment and yet a careful study of their published material shows that most of the successes have occurred in cases having no demonstrable evidence of cancer in the material removed. To many the removal of uninvolved tissue containing natural defense barriers is an unwarranted procedure, and the fact that it is accompanied by an appreciable operative mortality varying from 2 to 11 per cent in various clinics renders it even less desirable. In certain locations, such as the lip, the probability of the appearance of cervical metastases after the successful irradiation of a primary lesion of moderate size is little greater than the chance of dying on the operating table if radical surgery be done. All of these facts have had a definite influence on medical thought and when Pflueger[12] collected the opinions of thirty well-known authorities some five years ago he found two-thirds of them opposed to routine dissection in cases having no palpable nodes. The men consulted were Berven, Burnam, Cade, Eller, Grossman, Henry, Jones, Juul, Laborde, MacKee, Maisin, Paterson, Pfahler, Pirie,

* Read at the Thirty-Ninth Annual Meeting, American Roentgen Ray Society, Atlantic City, N. J., Sept. 20–23, 1938.

TABLE I

MALIGNANT PHARYNGEAL TUMORS WITH ADENOPATHY

| Patient | Primary Lesion | Pathology | Adenopathy | Therapy | Changes in Lymph Nodes | Outcome |
|---|---|---|---|---|---|---|
| C. P. | Pharynx | Transitional cell carcinoma | Large nodes both sides | 3900 r<br>3600 r | Resolution; no recurrence | Well 4 yr. |
| Mrs. O. N. E. | Tonsil | Epidermoid carcinoma, Grade 3 | Large node one side | 2700 r<br>1800 r | Resolution; no recurrence | Well 3 yr. |
| Mrs. C. | Pharynx | | Large mass one side | 2500 r<br>2500 r | Resolution; no recurrence | Well 2 yr. with resolution of intracranial extension |
| Mrs. M. | Tonsil | Lymphosarcoma | Large node one side | 2400 r | Resolution; no recurrence | Well 1½ yr. |
| J. E. W. | Post nares | Adenocarcinoma | Multiple submental | 2400 r radium needles | Resolution; no recurrence | Died in 2 yr. with internal metastases |
| Miss E. B. | Tonsil | Transitional cell carcinoma | Large mass one side | 600 r radium needles | Resolution; no recurrence | Died in 3 yr. probably from internal metastases |
| Mrs. W. | Pharynx | — | Large node one side | 3100 r<br>1750 r | Resolution; no recurrence | Well 2½ yr. |
| W. W. | Pharynx | Transitional cell carcinoma | Large masses both sides | 3000 r<br>3000 r | Resolution; no recurrence | Died in 1 yr. from internal metastases |
| N. T. | Pharynx | Transitional cell carcinoma | Large masses both sides | 2950 r<br>2950 r | Resolution; no recurrence | Died in 8 mo. from internal metastases |
| Mrs. F. K. | Tonsil | Lymphoepithelioma | Large nodes one side | 2300 r | Resolution; no recurrence | Died in 4 mo. with abdominal metastases |
| A. B. | Pharynx | Transitional cell carcinoma | Large masses both sides | 3300 r<br>2700 r | Resolution; no recurrence | Died in 1 yr. of internal metastases |
| F. A. | Pharynx | Epidermoid carcinoma, Grade 4 | Small submental | 2400 r | Resolution; no recurrence | Died in 1 yr. of intracranial metastases |

Richards, Simpson, Stebbing, Sutton, Wallace, Bloodgood, Coller, Handley, Hazen, Jeanneney, Jorstad, The Mayo Clinic, Morison, Pichler, Simmons and Greenough, and a summary of their opinions is shown in Table II.

TABLE II

OPINIONS OF 30 AUTHORITIES ON NECK DISSECTION

| | Glands Not Palpable | | Glands Palpable | |
|---|---|---|---|---|
| | Yes | No | Yes | No |
| Cancer of lip | 10 | 20 | 25 | 2 |
| Cancer of tongue | 11 | 19 | 24 | 3 |
| Cancer buccal mucosa | 7 | 22 | 21 | 3 |
| | 28 | 61 | 70 | 8 |

The real worth of any method should be judged by the results obtained from the treatment of cervical lymph nodes which actually contain cancer. If only five year results based on absolute figures are accepted, most surgical reports available to the author such as those of Crile,[2] Brewer,[1] Kennedy,[6] Simmons and Daland,[14] Wangensteen and Randall[16] and Moreland[11] must be rejected as incomplete. A few of the published figures for operated lip cases covering five year periods of observation are included in Table III. From this rather scanty material the conclusion might be drawn that only 1 case in 10 with malignant cervical nodes has a chance of cure with surgery. However, many factors influence the prognosis, and for this reason Quick[13] and Duffy[3] have carefully studied

Fig. 1. Reading from above downwards, these large epidermoid carcinomas of the face have been well for one year and four months, two years and seven months, and four years and seven months, respectively. They were treated exclusively by irradiation and no cervical metastases have appeared.

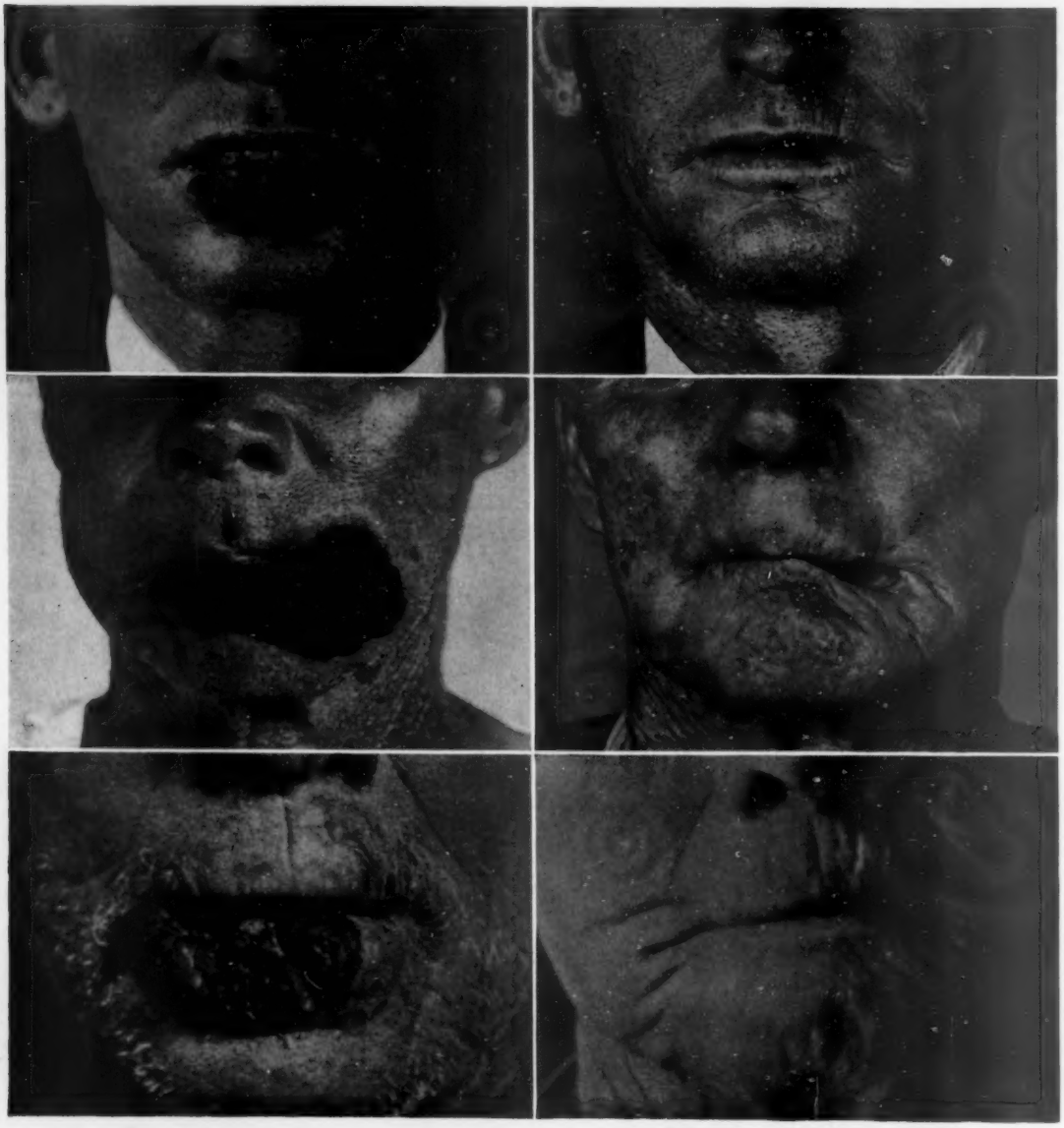

Fig. 2. Reading from above downwards, these large epidermoid carcinomas of the lip have been well for three years and seven months, three years and one month, and sixteen years, respectively. They were treated exclusively by irradiation and no cervical metastases have appeared.

the causes of failure and have published a set of indications and contraindications for operation. If only the favorable cases receive block dissections the salvage percentage accredited to the scalpel will undoubtedly show a sharp increase. Wile and Hand[17] report a small carefully selected group of lip cases in which about 40 per cent of the patients obtained five year cures with block dissections. However, if we assume the figures in Table III to be correct, about 90 per cent of the patients with cervical metastases will not respond favorably to this form of treatment.

The radiologist is called upon to care for these unfortunates and any headway that he may make is worth reporting. That his efforts are none too well received by those who are wedded to radical surgery is illustrated by the attitude of Fischel[5] who says: "Conclusive evidence that any method other than surgery is effective either in the

prevention of or the cure of cervical metastasis is lacking." The same author's unfamiliarity with irradiation becomes more evident as he continues: "Coutard presents the strongest case for radiology but he produces a terrific 'epidermitis' of the skin and tragic sequelae are noted." Many cases have received the modified Coutard plan of treatment in our own clinic but although regressions have occurred we have not seen a prolonged freedom from involvement of the glands in any patient belonging in our second group. Doses ranging from 3,600 r to 4,000 r, measured in air, have been administered but they cannot be recommended as curative. Doses of 600 r to 2,000 r advocated by many surgeons after neck dissections are therefore of comparatively little value.

TABLE III

CARCINOMA OF LIP

| | Author | Date | Without Cervical Glands | | With Cervical Glands | |
|---|---|---|---|---|---|---|
| | | | Treated | Alive 5 yr. | Treated | Alive 5 yr. |
| Irradiation Surgery | Lund and Holton | 1933 | 54 | 42 | 34 | 3 |
| | Broders | 1920 | 344 | 140 | 105 | 10 |
| | Sistrunk | 1921 | 98 | 84 | 11 | 2 |
| | | | 496 | 266 (53.6%) | 150 | 15 (10%) |
| Irradiation Alone | Kelly | 1933 | 82 | 67 | 36 | 2 (4 yr.) |
| | Pfahler and Vastine | 1932 | 197 | 186 | 39 | 21 |
| | Schreiner and Mattick | 1933 | 163 | 94 | 38 | 8 |
| | | | 442 | 374 (78.5%) | 113 | 41 (36.2%) |

The figures in Table III for patients with cervical glands treated with irradiation alone are probably too high because some of the nodes may have been of inflammatory origin, and this objection can be raised to most reports covering patients treated by non-surgical methods. However, the experienced observer cannot be wrong in every instance and these reports should not be totally ignored. The best five year statistics available to me are those of Tailhefer[15] who treated a group of 69 cases of cancer of the tongue having cervical metastases with a combination of neck surgery and irradiation. In each instance the primary lesion was treated with radium. Three weeks later a block dissection of the neck was done and followed by heavy doses of external irradiation, sometimes accompanied by implanted needles. Of this series, 12 cases (17.3 per cent) were living and well at the end of five years. The operative mortality was 4.3 per cent. Other surgeons have noted a lowered operative mortality when the neck dissection is not accompanied by a simultaneous surgical attack on the primary lesion.

Although Laborde[7] and others have advised against implanted radium in the treatment of malignant lymph nodes, the Memorial Hospital group has repeatedly advocated the use of radon seeds, and Martin and Sharp[10] boldly state: "After several years of experience with block dissections of the neck, we believe that implantation with gold seeds offers equally good end results in operable cases without the operative risk of the major surgical procedure." Although no statistics covering a sizable number of cases is cited by these authors, they describe one patient with extensive involvement on both sides that obtained a good five year result.

In viewing roentgenograms of the necks of cases treated with radon seeds we have

been struck with the lack of even spacing in the implantation patterns. Since the seeds are inserted with the tissues retracted at operation they can hardly be expected to maintain a fixed relationship to one another after the wound is closed. With this point in mind, a series of patients has been treated using long weak platinum radium needles of a type described in previous papers.[8,9] These needles can be inserted through small skin incisions and placed parallel to one another, 1 to 1.5 cm. apart in the submental, submaxillary or cervical regions, thereby insuring a fairly uniform irradiation. They are usually kept in place for seven days. This type of therapy has been effective in some instances, but in many the dosage apparently has been too small. Failla[4] has observed that the skin is spared to a considerable degree when large doses are administered partially with radium and partially with roentgen rays. For this reason roentgen therapy has been given cautiously to the needled areas in the neck with the needles in place in an effort to determine the largest dose tolerated by the normal tissues. This treatment has in most instances been administered at 220 kv., with 20 ma. flowing, using a filter of 2.0 mm. of copper and 1.0 mm. of aluminum and a target-skin distance of 50 cm. The portals never measure more than 15 cm. on a side. Daily doses of 350 r, measured in air, have been given until the

TABLE IV

LYMPH NODE METASTASES TREATED WITH IRRADIATION ALONE

| Patient | Primary Lesion | Pathology | Lymph Nodes | | | Therapy | Results |
|---|---|---|---|---|---|---|---|
| | | | Location | Size | Primary Healed | | |
| 1. S. C. S. | Face | — | Upper cervical | 2″×2½″ | 1 yr. | Radium needles 600 r | Glands resolved; well 5 yr. |
| 2. W. T. V. | Cheek | Epidermoid carcinoma, Grade 2 | Submaxillary | 1″×1″ | Appeared with primary | Radium needles 1500 r | Glands resolved; well 3 yr. 7 mo. |
| 3. W. A. C. | Lower lip | — | Submental cervical | 1½″ 1″ | 4 yr. | Radium needles 2100 r | Glands resolved; well 2 yr. 10 mo. |
| 4. G. M. M. | Face | — | Preauricular | 2¼″×2¼″ | 1½ yr. | Radium needles 1500 r | Glands resolved; well 2 yr. 5 mo. |
| 5. Mrs. W. H. M. | Cheek | Epidermoid carcinoma, Grade 2 | Three submental | All ¼″ | Appeared with primary | Radium needles 2100 r | Glands resolved; well 2 yr. 2 mo. |
| 6. Mrs. J. M. B. | Cheek | Epidermoid carcinoma, Grade 1 | Three cervical | All about ¾″ | 4 mo. | Radium needles 2100 r | Glands resolved; well 2 yr. 11 mo. |
| 7. Mrs. W. F. C. | Cheek | Epidermoid carcinoma, Grade 1 | Three preauricular | All about ¾″ to ½″ | Appeared with primary | Radium needles 2100 r | Glands resolved; well 1 yr. 3 mo. |
| 8. A. W. | Lower lip | Epidermoid carcinoma, Grade 3 | Two submental | Both ¾″ | Appeared with primary | Radium needles 2100 r | Glands resolved; well 1 yr. |
| 9. R. J. G. | Floor of mouth | Epidermoid carcinoma, Grade 2 | Cervical | ¾″ | 1½ yr. | Radium needles 2100 r | Glands resolved; well 10 mo. |
| 10. L. J. | Lower lip | — | Two submental | Both ½″ | Appeared with primary | Radium needles 2100 r | Glands resolved; well 9 mo. |
| 11. C. R. D. | Cheek | Epidermoid carcinoma, Grade 1 | Submental | ¾″ | 15 mo. | Radium needles 2100 r | Glands resolved; well 3 mo. |
| 12. H. M. O. | Lower lip | — | Submental | ¾″ | 1 yr. | Radium needles 2100 r | Glands resolved; died suddenly after 1 yr. 5 mo. |
| 13. W. B. P. | Lower lip | — | Submental | 2″ | Appeared with primary | Radium needles 2100 r | Small cyst remains; well 9 mo. |
| 14. J. H. K. | Lower lip | — | Submental | 1″ | 13 mo | Radium needles no x-ray | Good resolution; recurrence in 1 yr. |
| 15. F. F. C. | Lower lip | — | Submental | 1½″ | 1 yr. | Radium needles 2100 r | Untraced—probably dead |
| 16. J. T. H. | Tongue | Epidermoid carcinoma, Grade 2 | Submaxillary | 2″ | 3 mo. | Radium needles 1800 r | Untraced |
| 17. D. M. N. | Floor of mouth | Epidermoid carcinoma, Grade 2 | Upper cervical | 2″ | 3 mo. | Radium needles 2100 r | Glands improved; died 4 mo. later with spinal metastasis |

needled area has received 2,100 r. The combined therapy causes a marked reaction with some denudation in the center of the area, but healing is usually prompt and the healed skin resembles that subjected to heavy Coutard therapy. Some may consider this treatment heroic but experience has shown that epidermoid carcinoma growing in lymph nodes can be eradicated only when doses larger than those effective in the primary lesion are used. The method is particularly well suited for large masses in the neck where the even distribution of radon seeds is quite difficult. In such cases the large mass frequently changes slowly into a cyst filled with a clear yellow fluid which absorbs as the cyst shrinks.

Results in a series of 17 cases in which this technique or a slight modification was used are given in Table IV. The immediate results were known to be good in all but 3 cases and in 9 no recurrences were noted for a year or more. I am fully aware that this report will be criticized because of the absence of biopsies from certain of the primary lesions and all of the secondary lesions. Clinically, all of these patients were suffering from well-advanced malignant neoplasms about which few experienced observers would express any real doubt. Some will insist that all of the nodes had an inflammatory origin, but note should be taken of the fact that many of the larger glands appeared months and sometimes years after the complete healing of the primary tumors. This work is presented, not as a finished scientific treatise, but as a description of a technique well worth trying, particularly in those cases in which surgery offers little or nothing. Should the five year salvage prove reasonably high it is my belief that all patients with no palpable glands in the neck might profit by the implantation of the submental region and the submaxillary area on the involved side.

The following case history illustrates the technique and the immediate changes observed:

Case I. G. W., male, white, aged fifty-three, had observed a growing tumor on his lower lip for two years. No treatment of any sort had been attempted. For two months he had noticed two hard lumps in the submental region. They were never tender but were increasing rapidly in size.

Examination revealed a bleeding, elevated mass of friable tissue covering most of the lower lip and measuring 2.5×5 cm. Two hard nontender movable glands, each measuring about 2.5 cm. in diameter, were observed in the left submental region. The projecting portion of the tumor was removed with a high frequency loop and the pathological report on the removed tissue was epidermoid carcinoma, Grade 3.

Three 1.33 mg. platinum radium needles were inserted vertically into the center of the lip at 1 cm. intervals and four 1.33 mg. needles were inserted into each side of the lip in a horizontal direction using the same spacing. Four 2.4 mg. long needles were inserted into and alongside each of the glands in the submental region. These needles were placed parallel to one another at 1 cm. intervals so as to pretty well cover the region between the mandible and the thyroid cartilage in the midline and on the left side. All of the needles remained in place for exactly seven days.

On the day following the implantation, 350 r was given to the submental region and left side of the neck and repeated daily for six days, thereby administering 2,100 r. This treatment was given at 220 kv., with a current of 20 ma., a target-skin distance of 50 cm., and a filter of 2.0 mm. of copper and 1.0 mm. of aluminum to an area measuring 15 cm. on a side laid out to include the needles planted in the neck. When the needles were removed the neck was dressed with boric ointment and the patient returned to his home.

When he returned at the end of four weeks all evidence of both the primary lesion and the glands had disappeared. Denuded areas were seen on the lip and overlying the regions previously occupied by the glands. The result at the end of eight weeks is shown in Figure 3. The skin is now healed and although there is some puffiness in the subcutaneous tissues of the neck, no glands are palpable.

The next case indicates the protective action of the combined therapy in the submental region and illustrates the fact that small lesions in the mouth may metastasize to the lower cervical nodes early.

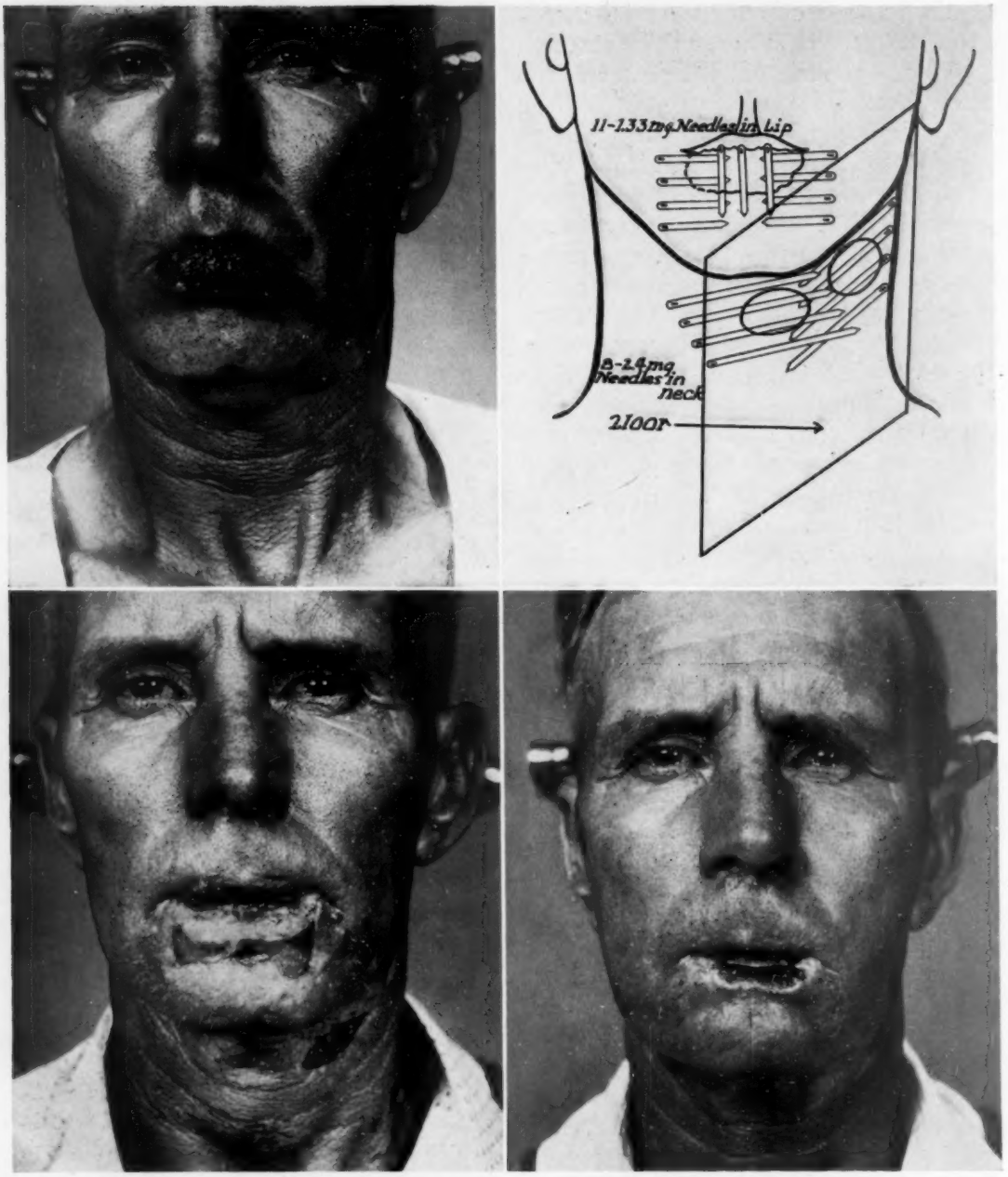


FIG. 3. Case I. Large epidermoid carcinoma of lip, Grade 3, with two submental glands each measuring 2.5 cm. in diameter, treated with the technique illustrated in the drawing. The radium needles remained in place for seven days. The lower photographs show the treatment reaction in one month and healing of the lip almost complete with disappearance of the glands at two months.

CASE II. R. J. G., male, white, aged forty-eight, had noticed a tumor growing in the floor of the mouth and involving the frenum of the tongue for about a year. Examination revealed a hard, flat, slightly elevated tumor with an ulcerated center, measuring 2 cm. in diameter, growing in the floor of the mouth exactly in the midline. A piece of tissue removed from the edge of the neoplasm was diagnosed as epidermoid carcinoma, Grade 2. No glands could be felt in the neck.

Seven 0.6 mg. radium needles were sewn in

a radial pattern beneath the lesion in the mouth and two 2.4 mg. and three 1.33 mg. needles were inserted at 1 cm. intervals deep in the submental tissues. All of the needles were left in place for exactly seven days. Square areas measuring 10 cm. on a side were laid out on either side of the submental region and daily doses of 300 r were given to alternate sides beginning on the day after the implantation. These treatments were given with 220 kv., a current of 20 ma., a target-skin distance of 50 cm., and a filter of 0.8 mm. of tin, 0.25 mm. of copper and 1.0 mm. of aluminum, and were continued until each area had received 1,800 r.

A rather marked reaction occurred in the mouth but at the end of two months the lesion was smoothly healed. There was some puffiness of the tissues under the chin but no glands were palpable. He returned one and a half years after he was treated stating that he had gained 40 pounds and felt unusually well. The mouth was smoothly healed and no submental nodes could be palpated. However, a single hard gland measuring 2 cm. in diameter could be felt in the midportion of the left side of the neck at the anterior edge of the sternomastoid muscle. It was fixed to the underlying tissues.

The gland was impaled with a 2.4 mg. long radium needle placed horizontally in the neck and three similar needles were inserted above and three below it at intervals of 1.0 cm. All of the needles were inserted deep into the tissues and placed parallel to one another. They were left in place seven days and on each of the last six days an area measuring 15 cm. on a side covering the lower left neck received 350 r given at 220 kv., with a current of 20 ma., a target-skin distance of 50 cm., and a filter of 2.0 mm. of copper and 1.0 mm. of aluminum.

The reaction was severe and a denuded area measuring about 6 cm. in diameter appeared over the gland. However, healing was complete in two months. At the end of ten months the treated skin is soft and pliable but shows a marked lack of pigment. No glands can be felt in the neck and the patient is in excellent health two years and four months after the treatment of the original lesion.

The following case history illustrates the good results that may be obtained with irradiation in Grade 1 epidermoid carcinoma even when glands appear:

Case III. Mrs. J. M. B., white, aged seventy-

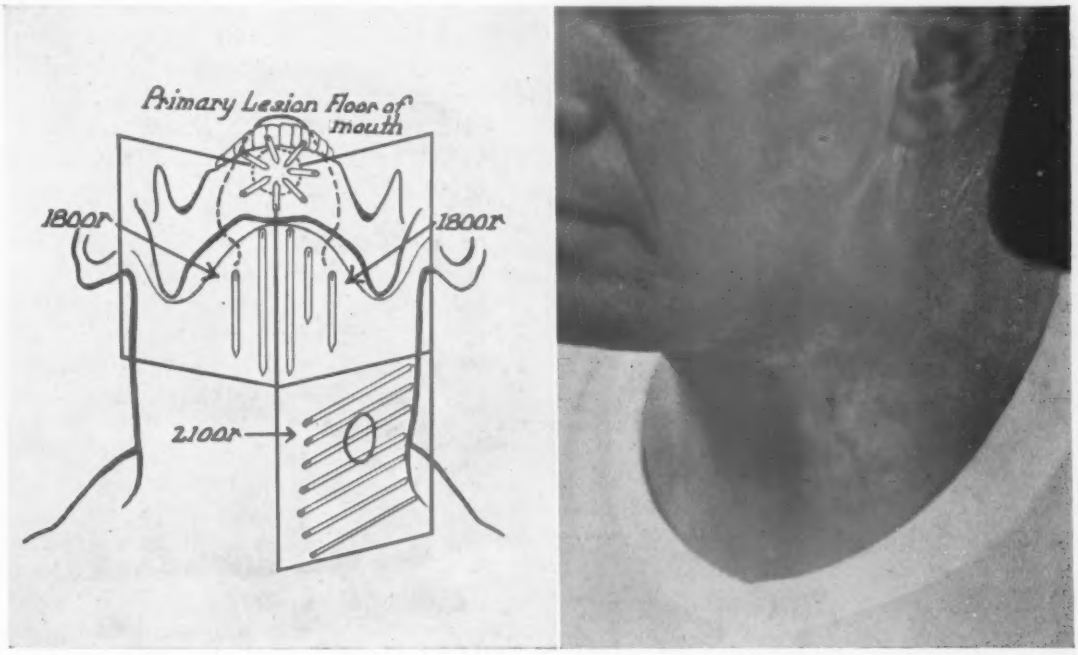


Fig. 4. Case II. The technique in the upper half of the drawing was given to a small epidermoid carcinoma, Grade 2, in the floor of the mouth. The needles remained in place for seven days. The submental area remained clear but a single gland appeared in the side of the neck one and a half years later. The technique in the lower half of the drawing was used and the gland disappeared. The depigmentation of the skin as it appeared ten months later is shown in the photograph.

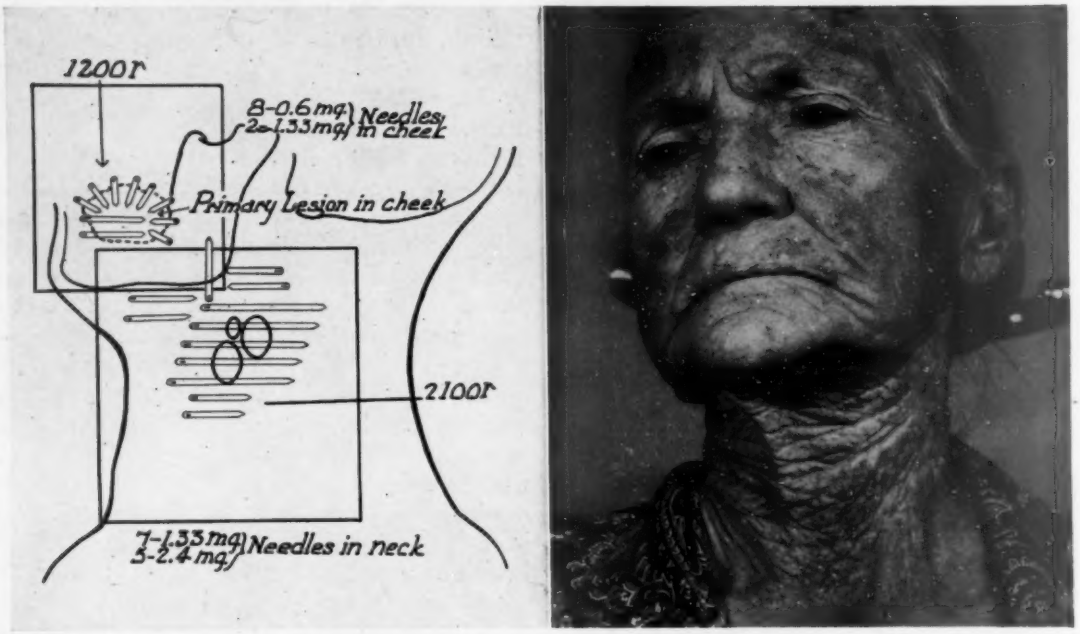


Fig. 5. Case III. A "snuff dipper's" carcinoma of the cheek, Grade 1, cleared up when treated as shown in the upper half of the drawing. Three hard glands appeared in the neck four months later and were treated as shown in the lower portion of the drawing. The slight scarring of the neck remaining after three years is shown in the photograph. No glands are now palpable.

two, had "dipped" snuff since the age of five. For four months she had noticed a hard non-painful lump inside the left cheek. Examination revealed a tumor measuring 2.5 cm. in diameter in the mucous membrane of the left cheek. The teeth were missing and the lower edge of the neoplasm overlapped the gum margin. The pathological report on a piece of tissue from the edge of the lesion was epidermoid carcinoma, Grade 1. No glands were palpable in the neck.

Eight 0.6 mg. and two 1.33 mg. radium needles were stitched under and around the edges of the tumor and left in place for seven days. Daily doses of 300 r were administered to a 10 cm. square overlying the left cheek and submaxillary area until 1,200 r had been given. The factors used were 220 kv., 20 ma., a target-skin distance of 50 cm., and a filter of 2.0 mm. of copper and 1.0 mm. of aluminum.

At the end of six weeks the tumor was gone and the cheek was smoothly healed but at the end of four months she returned with a group of three hard, non-tender glands in the upper anterior cervical region, each measuring about 2 cm. in diameter. There were no submental or submaxillary glands felt. Five 2.4 mg. and seven 1.33 mg. radium needles were planted in and about the glands in the neck in a parallel pattern and daily doses of 350 r were given to a square area measuring 10 cm. on a side laid out to include the upper left cervical region. The factors used were 220 kv., 20 ma., a target-skin distance of 50 cm., and a filter of 2.0 mm. of copper and 1.0 mm. of aluminum. At the end of a month the treated area was denuded in its central portion and the glands were much smaller. Healing was very slow in this patient, probably because of her age, and the treated skin required six months for complete healing. However, all evidence of enlarged glands disappeared and she looks and feels quite well three years after the treatment of the neck. There is some scarring and lack of pigment in the skin on the left side, but it is soft and pliable.

Case IV. W. T. V., male, white, aged sixty-eight, had chewed tobacco for many years and had noticed some soreness in the right cheek for about seven years. For two months he had been able to feel a hard mass in the right cheek.

Examination showed the mucous membrane of the cheek covered with a leukoplakia. An irregular mass of friable tissue was seen in the lower cheek adjoining the gum margin and a

biopsy specimen from this region revealed epidermoid carcinoma, Grade 2. A hard gland measuring about 2.5 cm. in diameter was felt in the submaxillary region.

Four 1.33 mg. radium needles were sewn under the lesion inside the mouth and seven long 2.4 mg. needles were inserted into the cheek and submental region. Four 1.33 mg. needles were placed vertically in the submaxillary region and the entire pattern remained in place for seven days. On each of the last five days 300 r was administered to a 10 cm. square laid out over the right jaw and upper cervical region using 220 kv., 20 ma., a target-skin distance of 50 cm., and a filter of 2.0 mm. of copper and 1.0 mm. of aluminum.

At the end of two months there was still a little radium reaction on the side of the tongue but the lesion in the cheek had healed and the submaxillary gland was no longer palpable. At the end of six months he returned with two small recurrent lesions on the upper right gum and soft palate. Biopsies showed these lesions to be epidermoid carcinoma, Grade 2. Seven 0.6 mg. and one 1.33 mg. radium needles were sewn under these lesions for seven days and they promptly disappeared.

Three years and seven months have now elapsed since the first treatment was given and the patient feels quite well and shows no evidence of carcinoma in the mouth or neck.

Case v. W. A. C., male, white, aged fifty-two, had noticed a hard mass in the middle of the lower lip for about a year and it was growing steadily. It received six doses of low voltage roentgen rays (85 kv.), each amounting to about 800 r, on alternate days over an area slightly larger than the tumor, which measured about 2.0 cm. in diameter. No biopsy was done but the clinical diagnosis was cancer. At the end of two months, the lip was smoothly healed. About four years later he noticed some "kernels" growing under his chin but allowed them to grow for a year before returning for treatment. When he finally returned five years after the treatment of the primary lesion, an egg-shaped gland measuring about 7 cm. in length was felt occupying most of the mid-submental region and a smaller mass about 5 cm. in length was felt in the upper neck just to the right of the one in the midline.

Eight 2.4 mg. and five 1.33 mg. radium needles were placed in and alongside the glands for seven days and on each of the last six days 350 r was given to a 15 cm. square including the right neck and submental region. The factors used were 220 kv., 20 ma., a target-

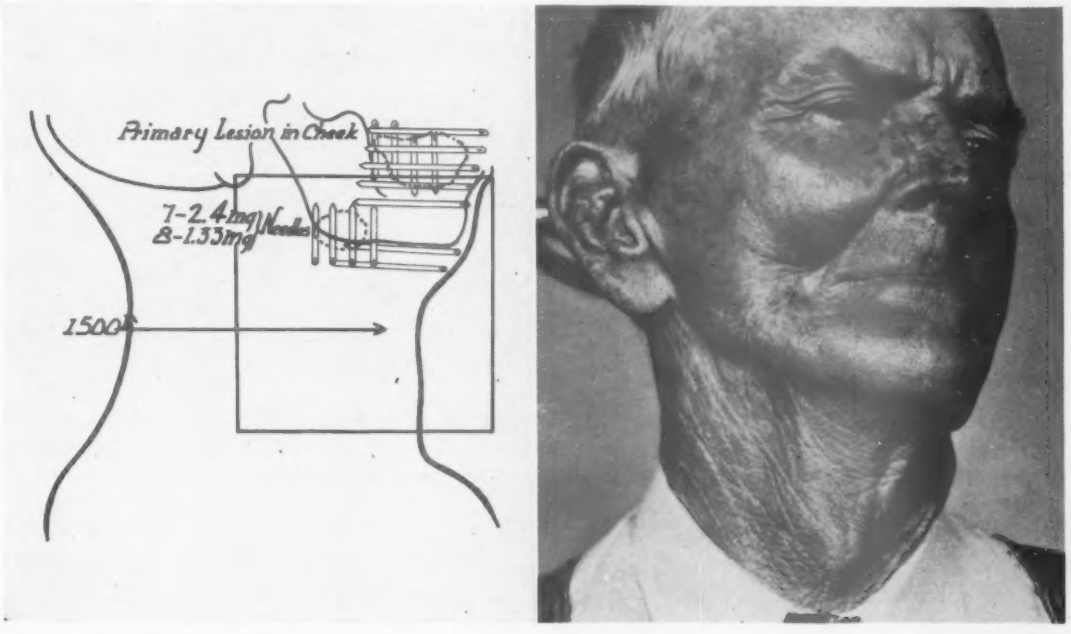


Fig. 6. Case iv. Epidermoid carcinoma, Grade 2, of inside of cheek with a large submaxillary gland treated with the technique shown in the drawing. The appearance of the neck and face three years and seven months later when he appeared to be perfectly well are shown in the photograph.

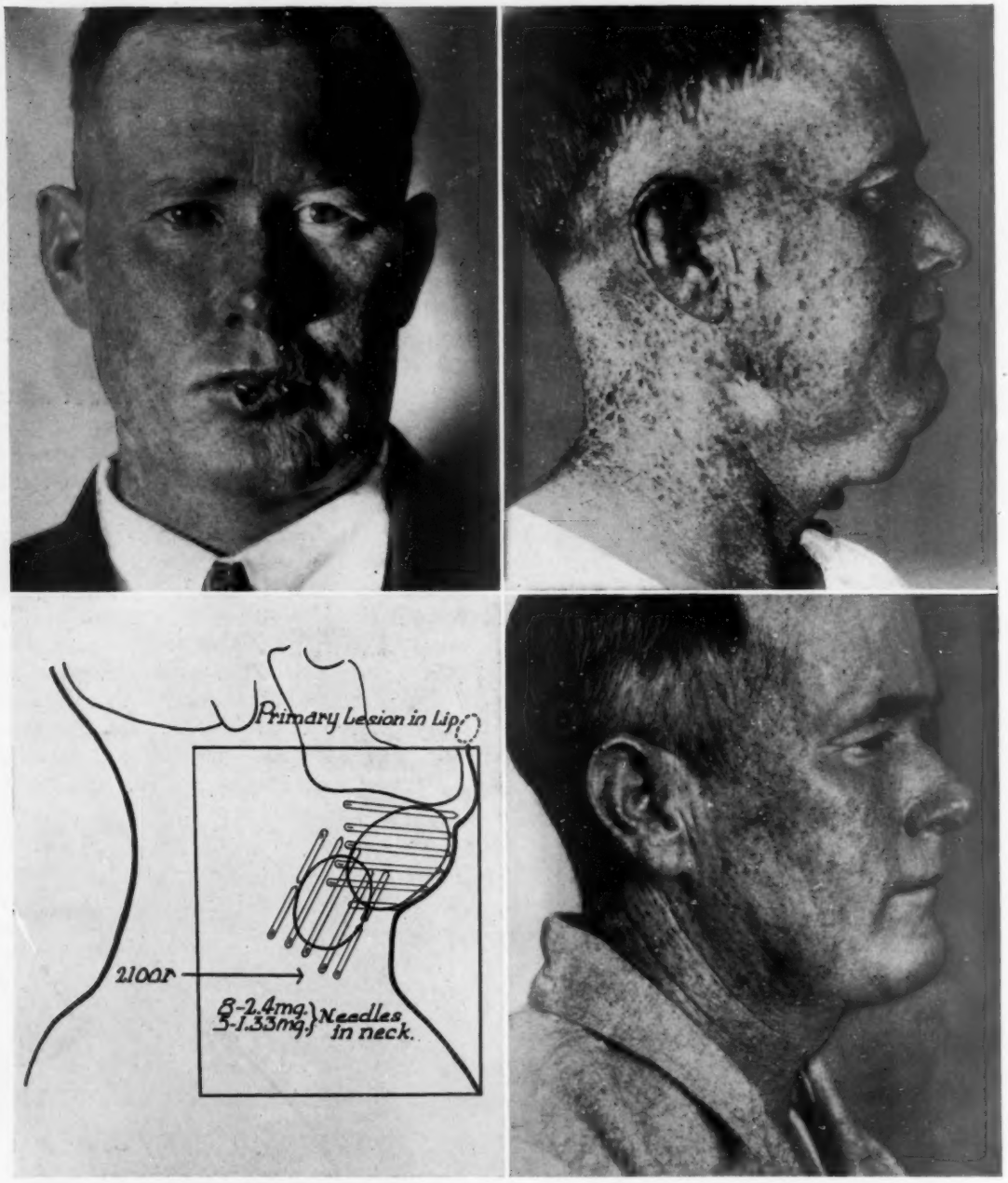


FIG. 7. Case v. The large glands shown in the neck in the upper right photograph, appearing four years after the irradiation cure of the carcinoma of the lip illustrated in the upper left photograph, were treated with the technique shown in the drawing. The lower photograph was made two years and ten months after the treatment when no glands could be palpated.

skin distance of 50 cm., and a filter of 2.0 mm. of copper and 1.0 mm. of aluminum.

When the larger gland was punctured, cheesy material oozed out and there was some drainage from the puncture wounds for about six weeks. At the end of three months the glands were completely shrunken and there was some scarring under the chin. The neck is still smoothly healed two years and ten months after the radium implantation and the patient looks and feels quite well.

SUMMARY

1. Malignant cervical lymph nodes secondary to radiosensitive tumors primary in the throat should be treated exclusively by irradiation.

2. Block dissection has cured only a small number of patients (approximately 10 per cent) in which the cervical nodes actually contain epidermoid carcinoma and the procedure is accompanied by an appreciable operative mortality.

3. A combined roentgen and radium technique is described which has proved effective, especially in the care of the larger metastatic cervical nodes secondary to primary lesions of the face, lip and mouth.

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DISCUSSION

DR. DOUGLAS QUICK, New York City. We are indebted to Dr. Martin for this contribution, one more directed toward the conservative handling of metastatic lymph nodes.

In presenting statistics of the earlier radical surgery of the neck, I think we must remember something of the conditions under which that earlier surgery was done. There was no good irradiation in a larger group or range of cases available at that time. The operative mortality was necessarily high. It is certainly less today, by a good deal, particularly on account of anesthesia.

I say all this because I think it is only fair to judge those surgical case statistics in that light, and I say it because, as you know, I am not an adherent of radical neck surgery. I think my last publication on neck nodes was made about 1934, and there I outlined one group in which I was still an adherent of complete unilateral dissection. I think in the interim I have become more conservative, even in that group, although I think there is here and there a case where, following the preliminary irradiation, complete resection should be done.

Statistics are likely to be very misleading in such a varied and complicated group of cases unless they are most painfully exhaustive in the analysis of the disease. The varying groups and types, locations, whether bilateral or unilateral, and all that sort of thing should enter into the analysis if it really is going to be instructive and not misleading. However, radiation therapy is improving, gaining ground and being better done.

There are a number of points on which I must say I disagree with Dr. Martin in his method which he has presented this morning.

First, all nodes from the hypopharyngeal growths cannot be left to external irradiation of the type now generally employed at 200 kv. Many of them do disappear very satisfactorily. They may remain so for a year or more. Then they are apt gradually to recur. When they do that, the best chance to have handled them permanently has been passed. They may recur up to much more than a year later, but certainly within that period most of them do.

Dr. Martin himself implies adherence to Coutard's principles, but in cases which he has cited in this group, it does not seem to me that he employs those principles. I am convinced that his external therapy results would be better if he did adhere more closely to those principles of treatment.

My experience with Grade 4 nodes in the neck is that they are the only group that is really safe when left entirely to the regular, well-done 200 kv. therapy.

Another point is that Dr. Martin rather deplores the elaborate descriptions of technical detail without supporting statistics, and I infer from his paper, which I had the pleasure of going over only recently, that he referred to surgical technique. I must say that I believe the surgical technique cannot be too carefully attended to and stressed even though it is a simple procedure. I mean by that the exposure for implantation. Certainly, the radical dissection, well done, is not a simple procedure. But we are not discussing that here this morning.

Premature statistics on radon implantation are, in my opinion, worse than useless because they are apt to be misleading to those who will see little of this work and, of course, as he noted in his manuscript, statistics unsupported by verifying histology carry only a limited conviction; especially to those who are not actually doing the work.

I am wholly opposed to using needles or seeds through skin puncture. The neck is anatomically too "busy" a place to be subjected to blind trauma. The structures, particularly along and within the carotid sheath, are very, very important structures. I have seen necks opened surgically in the sincere belief that a metastatic node was palpable, in the more common location, in an elderly patient, only to find that it was an enlarged and calcified carotid bulb. The carotid bulb has actually been punctured by a needle by an inexperienced operator with the neck exposed. I think Dr. Martin is very fortunate that he has so far missed the carotid bulb with one of his long needles.

In my judgment, if a node is too big to require accurate localization by exposure for implantation, it is too big for implantation and should best be left to good external therapy.

I regard his roentgen irradiation alone as too heavy in the daily quantities stated through such a large field as he has outlined; that is, 15 by 15 cm. in some of the cases at least. It is given too quickly; that is, over a seven day total period. When you add to that the intensity from the radium in the needles which are present at the same time as these exposures are being made, it runs it up pretty high. I should not object to the intensity of the skin reactions if it meant complete control of the more fully differentiated growths in nodes by external therapy alone but it is not necessary where implantation is done also.

I have recently seen a group of cases, not of the anaplastic type, but the more completely differentiated nodes, that have been very heavily treated by 400 kv. roentgen irradiation alone and where the skin reactions are temporarily very severe, and I have been very much impressed by them. The regression seems to be very complete in every detail.

In dealing with this newer, supervoltage therapy, I think we have reason to expect substantial improvement in technical detail in the future. I am happy to go along with that work and with that type of irradiation in the hope that we can handle these by external therapy alone. But, if it means getting these very severe reactions with the 400 kv. or with any voltage for that matter, and then having to open the neck to do some type of subcutaneous trauma as well, then I doubt if it will prove satisfactory either to our American lay public or to our American professional public.

At the present time, I am still convinced of the superiority of the simple, accurate surgical exposure under local anesthesia, accurate seed placement, direct needle aspiration of nodes for tissue histological verification, and for drainage of any central liquefaction debris. (Many of these nodes are centrally liquefied and if implanted with this debris still present, are apt to produce a very sharp and unnecessary inflammatory reaction added to the irradiation reaction.) Then the plain, simple, clean closure of the wound, making a neat job of it from beginning to end.

Dr. Martin (closing). I am very glad that Dr. Quick has spoken frankly about our new technique. I have the greatest admiration for the work that he and his associates have done at the Memorial Hospital in the treatment of metastatic cervical glands and deeply value his criticism.

His contention that the accuracy of implantation is improved by placing seeds in the glands at operation is not borne out by roentgenograms made afterwards. Usually the pattern observed after the closure of the wound is most irregular. It is true that the radiation is concentrated in certain involved nodes but our plan tends to deliver a uniform efficient dosage over a larger lymphatic distribution and should head off microscopic implants before they become palpable. If this procedure proves to be effective it will be of great value as a routine procedure in the treatment of the neck in patients with intraoral malignant tumors not accompanied by palpable adenopathy.

Dr. Quick is concerned about the danger of puncturing a large vessel with the long, blunt radium needles. I have placed them in every portion of the cervical region during an experience covering five years, and have never encountered this difficulty. The observation of a few simple rules and an average knowledge of anatomy will, I believe, render this danger negligible.

Dr. Quick also thinks that the roentgen therapy is given too rapidly. I have seen many cases of carcinoma completely cured with doses of radiation given within a week. The normal tissues show a generalized puffiness for a long period after the treatment is administered but this is a small price to pay for the elimination of cancer in the cervical lymph nodes.

The results obtained form the only worth while argument in favor of any method, and after some of you have tried this technique I hope you will share my enthusiasm. Certainly we need more effective methods in this field.

# RÔLE OF RETICULO-ENDOTHELIAL SYSTEM IN CANCER

## WITH REFERENCE TO CONGO RED THERAPY IN ROENTGEN SICKNESS AND ANEMIA*

### PRELIMINARY COMMUNICATION

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IN THE struggle of the organism against infection and malignant disease, as well as during the period of eliminating nuclear material from the blood, much depends on the readiness of the reticulo-endothelial system to respond. This system is generally regarded as being especially concerned with the defense of the body against living and non-living toxic agents, whether by the process of antitoxin formation or by phagocytosis. This term was first introduced by Aschoff in 1924, as a collective name of a system of cells distributed throughout the body and especially demonstrated by methods of *intra vitam* staining. By this term, we mean the reticular tissue in general and the phagocytic cells of the spleen, pulp, bone, marrow, lymph glands, and Kupffer cells of the liver, in particular (Sacks,[40] Jaffé[18]). The reticular tissue of endocrine glands seems to play an important part in the defense of the mechanism, also.

This system differs from the other organs of the body in that the reticular elements are not aggregated into a single organ, but are distributed throughout the body. Certain of the reticular cells would appear to be capable of remaining either fixed or ameboid in movement, depending on circumstances. It seems that the reticulo-endothelial system is extremely sensitive and its balance is easily disturbed under the influence of certain factors. All sorts of infections, although they may be strictly localized phenomena, reflect on the reticulo-endothelial system, often being responsible for tendencies toward hemolysis, hemorrhagia, and deviations in the blood picture.

Thus, hemochromatosis in secondary anemia as well as endothelial phagocytosis (clasmatocytosis) are but reflections of a disturbed activity of the reticulo-endothelial system.

The rôle which the reticulo-endothelial system plays in resistance to malignant disease seems to be of prime importance. There appears to be a general agreement that in some form or other the protective mechanism against malignant disease depends upon this system.

The work of Ludford,[24] Foulds (1932), Zacherl,[53] Brannstein (1931), and Brüda,[7] as well as many others, points out that the resistance to formation of tumors may break down when the reticulo-endothelial system is blocked and its activity decreased. For instance, it was shown that the resistance to the growth of transplanted tumors could be increased either by a previous tumor growth or by the injection of such material as embryonic skin. Naturally the question has been raised as to whether it would be possible to produce cancer immunity by stimulating the activity of the reticulo-endothelial system by roentgen irradiation or by some vital dye.

#### EFFECTS OF IRRADIATION

The effects of roentgen irradiation upon the reticulo-endothelial system has been the subject of intensive investigation by many authors. It has been established that this system is very sensitive to radiation, the post-irradiation effect depending entirely upon the dose applied. A small dose of radiation stimulates it, increasing its protective properties. A larger dose, on the contrary, inhibits or destroys the defense

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mechanism of the reticulo-endothelial system. This seems to be equally true of the infection or malignant condition concerned. "All writers upon this subject appear to concur in the view that in order to secure beneficial effects from radiation, in cases of microbial inflammation, it is essential that the dose administered should be a small one" (Colwell[12]). Speaking of their experiments, Mogilnitzky and Podljaschuk[30] report that the "so-called hemato-encephalic barrier is especially interesting in this respect. It is a well-known fact that the hemato-encephalic barrier constitutes a protection in the central nervous system against toxic agents circulating in the blood. Repeated doses of roentgen rays (150 kv.) applied to rabbits and dogs destroyed this protective barrier and degenerative atrophic changes appeared in the mesenchyme apparatus. With divided dosage the hemato-encephalic barrier remained unshocked."

Considering the fact that the reticulo-endothelial metabolic apparatus seems to be intimately connected with the formation of cholesterin (Landau and McNee[22]), this whole question acquires practical importance in radiation therapy. Since we are more and more convinced that malignant disease, even in its earlier stage, is not only a local disease, but a general disturbance of cellular dynamics, we cannot neglect the possible effect of local irradiation upon the general health and the reticulo-endothelial system in particular, the resistance to malignancy and to the metastasis depending, to a great extent, upon the state of the reticulo-endothelial system and on its response to malignant growth.

Experiments on animals indicate that a small dose of general irradiation increases the organism's resistance to the growth of transplanted tumors. Maximum resistance seems to be reached three to four weeks after the irradiation. The animals which received the preliminary irradiation showed signs of increased function of the reticulo-endothelial system; these changes consisted in the formation of histiocytic foci in the liver and a diffuse hyperplasia of Kupffer's stellate cells and of the reticular system of the spleen (Chambers and Scott,[11] and others).

These extensive experimental data, obtained by numerous authors, did not result in any practical solution, as far as radiation therapy is concerned. The radiotherapist is still confronted with the peculiar manifestation of the after effects of the local irradiation of patients. Although Coutard's technique considerably decreases the possible depressive effect from irradiation, yet signs of damage to the reticulo-endothelial system may often be observed in everyday practice. The absence of a sufficiently effective method of stabilizing the reticulo-endothelial system and therefore of increasing the resistance of the organism to metastasis seems to be a considerable handicap in our efforts to treat malignant disease successfully and to prevent metastasis.

In search of a method or substance which might act as a stabilizer of the reticulo-endothelial system, we have studied the effect upon the reticular apparatus of Congo red, a mono-azo dye. Our experiments have extended into the field of the interrelation existing between the activity of the reticulo-endothelial system and the resistance to malignant disease. Roentgen sickness and roentgen anemia, being common manifestations resulting from irradiation, have been investigated by us in connection with our studies.

### CONGO RED AS A HEMOSTATIC

The activity of the reticulo-endothelial system can be tested by its absorptive properties. Adler and Reimann[1] first introduced Congo red for testing the state of the reticulo-endothelial system. According to these authors, 80–100 cc. of a 1 per cent solution of Congo red injected intravenously is almost immediately eliminated from the blood by the liver and spleen. Jaffé and Berman (1928) pointed out that bile also participates in the elimination of dye, being particularly attracted by the

electronegative substance. Using the Adler test, Pohle and Davy[38] established that irradiation (150 r) of the spleen, one hour previous to the injection of dye, produces a more rapid elimination of the dye.

Bedson, Koster, Osseladore and Sacchetti, experimenting independently, found that, upon intravenous injection of suspensions of dye substances with electronegative charge (India ink), the number of blood platelets increased and the coagulation time diminished. At the same time they also noted an increase of the fibrinogen in the blood.

However, Wedekind[51] was the first, who in 1928 using a solution of Congo red—an electronegative colloidal dye—for a qualitative diagnosis of pulmonary tuberculosis, noted that Congo red had hemostatic properties. This incidental discovery was analyzed by Becker and Wienert, and they suggested the use of Congo red for all forms of hemorrhages.

Wedekind, Becker and Wienert[10] used 10 cc. of a 1 per cent solution of Congo red. The intravenous injection of this dye never gave rise to any disturbances. The number of cases treated by these authors was about 50, the patients suffering from various forms of hemorrhages, e.g., hemorrhages due to pulmonary tuberculosis and bronchiectasis, hemorrhages due to pleurisy, hemorrhages following extraction of teeth, hemorrhages due to cancers or ulcers of the stomach. The coagulation time was shortened in all of the cases and there occurred an increase in the number of platelets amounting to double or triple the initial number by the fifth or sixth day; subsequently the number of platelets diminished slowly and they reached the initial figure about three weeks later.

The injections were made slowly before breakfast in a vein of the elbow. *The important factor in both cases was that the injections caused no complications whatever.*

This hemostatic property of Congo red is due to the fact that negative electric charge upon introduction into the reticuloendothelial system of the various organs and tissues exercises a stimulating or paralyzing action, depending on the dosage. This effect is accompanied by changes of the anatomical structure of the reticuloendothelial system and by variations of chemical and physical elements of the circulating blood, affecting the albumin, globulin, fibrinogen, monocytes and platelets. Since the histiocytic elements play an important part in the regulation of the platelets, a function which is translated by a destruction of the platelets in case of excess, the extirpation and functional limitation of certain organs would consequently result in an increase of the platelets. One of the most important organs in this respect is undoubtedly the spleen. It is therefore possible that the hemostatic action of Congo red may be related to a limitation of the function of the organ which is charged with the regulation of the platelets in the blood.

After Wedekind's discovery, the therapeutic effect of Congo red was confirmed by a great number of authors in this country as well as abroad. Thus, Trossarelli[47] reported successful treatment of 2 patients who suffered from Werlhof's disease. A number of injections of coagulation substances had been tried in vain in both cases. The patient in the first case had refused to undergo a splenectomy; in the second case this operation could not be performed because of a serious concomitant affection of the heart. In view of the good results obtained by Wedekind, Becker and Wienert, the author decided to try injections of 1 per cent solution of Congo red.

The comparative study of these 2 cases showed that the quantities of the dye which were necessary in one and the other case differed. In the first case 24 cc. was used before the hemorrhagic diathesis was corrected, while in the second case it was necessary to use almost double that amount. Amantea[4] also reported the therapeutic effect of Congo red in Werlhof's disease.

Waldorp and Alvarez[49] believe great benefit may be derived from Congo red therapy

in various forms of hemorrhage. They have made successful use of it in hemorrhages due to affections of the kidneys.

They report the cases of 2 brothers in whom the efficacy of Congo red was demonstrated when injected intravenously in one case and intramuscularly in the other in doses of 1 cc. for each 8 or 10 kg. of body weight. The Congo red did not act on the oscillations of the time of coagulation, but it proved to be more effective than any measures previously tried in these 2 cases in treating hemophilic complications. The hemarthrosis was considerably alleviated. It was further noted that the 2 brothers did not present any hemophilic complications for one year after the Congo red treatment. Agranat,[3] Behr,[6] Bruno[8] and Perez de los Reyes[37] also confirmed the hemostatic properties of Congo red.

Several authors have treated pernicious anemia with considerable success using Congo red. Massa and Zolezzi[26, 27, 28] noted that Congo red injections produced an effect quite similar to that of liver extract. The red blood cells were increased from 1.5 million to 4.5 million with hemoglobin from 37–50 per cent to 93 per cent in a period of six weeks after ten to fifteen injections. Massa and Zolezzi continued treatment until blood regeneration was complete in 9 of the 14 cases which responded to Congo red, but it was felt that liver therapy was less troublesome to administer for continuous management. Massa and Zolezzi suggest that the dye prevents hemolysis by blocking reticuloendothelial cells. Congo red injections are of particular value in toxic hemorrhagia. Lendvai[23] also reported satisfactory results in treatment of pernicious anemia with this dye.

Mermod[29] confirmed these observations of Massa and Zolezzi. His observations were made on 2 cases of untreated but mild Addisonian anemia, using intravenous injections of 1.5 per cent Congo red in 6 per cent solution of dextrose. One patient received 60 cc. in five days, the other 90 cc. in ten days; both had a rise in reticulocytes and a fall in serum bilirubin comparable to that produced in similar cases by intramuscular injections of liver extract. Experimental studies on animals indicate some similarity between liver and Congo red action on reticulocytosis.

Many normal guinea pigs exhibit a slightly delayed but sharp and sustained reticulocyte shower following injection of liver extracts known to be potent in pernicious anemia. This response seems specific for the liver fractions valuable in therapy.

Congo red injected daily for five days into the peritoneal space of guinea pigs produced a reticulocyte shower maximal from five to seven days after beginning treatment with 30 mg. of dye per pig daily. The reticulocytosis declined gradually, reaching the control level from ten to fourteen days after the peak. At that time large doses of potent liver extract were injected, but caused no further reticulocyte response. Congo red not only produces the same effect on normal guinea pigs as potent liver extract, but the treatment, like that with liver, renders the animals refractory to liver therapy for a considerable period of time.

Hernández Díaz[16] reported satisfactory results with intravenous injections of a 1 per cent solution of Congo red. The interval between the injections was twenty-four hours.

As a rule, the hemorrhage stops after the first or second injection, except in rare cases in which four or five injections are necessary to control it. The treatment is indicated in any type of hemorrhage, but the best results are obtained in those of moderate intensity. The injections of Congo red are generally well tolerated. The febrile reaction following the injection shown by a small group of patients seemed to be due to a slight precipitation of the solute in the solvent, owing to the fact that Ringer's solution was used instead of distilled water in the preparation of the solution.

In the author's group of 64 patients, 58 were suffering from tuberculous and non-

tuberculous hemoptysis. Of these, the treatment failed in 2 cases of ulcerous tuberculosis with cavitation; gave mediocre results in 7 and succeeded in 49 (control of the hemorrhage after one, two or three injections without recurrences).

The phenomena observed in the blood after the injection are monocytosis, increase of the fibrinogen and of the platelets, and shortening of the time of coagulation.

Grasso,[14] considering the constantly good results of Congo red as a coagulant, proposed to try it in cases of icterus by retention and in adynamic icterus. A great number of coagulants have been proposed in icterus considering the great importance of the hemorrhagic diathesis in the preoperative and postoperative periods.

Grasso used Congo red in 1 per cent solutions, using 5 cc. for each injection, and in some cases 10 cc. daily. The injections were usually made intravenously, this method being preferred by most authors; in 2 cases it was necessary to make a deep intramuscular injection in the gluteal region. The intramuscular injections were not very painful and were easily tolerated, and no general or local reaction occurred so that they could be repeated several times. In no case, irrespective of the path of injection, were any accidents noted, either immediately or later. The soft perivenous parts always assumed a deep scarlet color.

The comparative study of the clinical and experimental data (the experiments being carried out on sick rabbits) showed that, in affections of the liver with icterus and prolongation of the time of hemorrhage, and more rarely of the time of coagulation, the Congo red was able to shorten the time of hemorrhage reducing it to normal limits, while a doubtful action, or, at least, a minimal action was exercised on the coagulation time. *The anti-hemorrhagic action was almost immediate* and could be noted first a few hours after the first injection; it was only transitory, however, since, it disappeared a few days after the treatment. In the rabbits treated with novirudin, the Congo red shortened the time of hemorrhage but only slightly influenced the coagulation time. The author found that it was best to use 1 per cent solutions in distilled water, using 5 cc. of Congo red intravenously; however, 10 cc. could be injected in single doses daily, and the injections were effective also intramuscularly. *The dye was tolerated by all patients and its use did not contraindicate the use of other drugs for symptomatic cures.*

The author does not venture a definite opinion regarding the mechanism of action of Congo red, considering that the question of hemorrhagic diathesis in affections of the liver is a difficult one.

Severe intestinal hemorrhage is one of the gravest complications of typhoid and, in order to control it in several complications of typhoid that were under his treatment, Szirmai[46] employed intravenous injections of Congo red. He points out that Congo red belongs to the electronegative, neutral, high molecular dye stuffs. In experiments it was proved to be nontoxic, and it was found to increase the blood platelets, the monocytes and the coagulability of the blood.

Szirmai employed Congo red in 10 cases of typhoid with severe intestinal hemorrhages. In 4 cases a single intravenous injection of 10 cc. of a 1 per cent solution stopped the hemorrhage, while in the other 2 cases, two or three injections were necessary. The repeated injections are given at intervals of twelve or twenty-four hours.

Aside from mild attacks of chills that developed in 2 patients, there were no harmful results from Congo red.

Congo red has proved to have a very definite use in pulmonary hemorrhage, according to experiments of Morlock and Pinchin.[31] The use of opiates is not without danger and this applies to any drug, assert these authors. They could arrest the pulmonary hemorrhage by a few injections of Congo red.

Numerous drugs have been employed in the treatment of gynecological hemorrhages; the very multiplicity recommended

for this purpose indicates that as yet a drug which possesses all the necessary properties for cases of this type does not exist. Kittner[20] discusses the therapeutic use of Congo red in the treatment of gynecological hemorrhages.

Congo red has hitherto been employed by Kittner in 71 cases of menorrhagia and metrorrhagia of various geneses. In most cases a single intravenous injection of 10 cc. of a 1 per cent solution was given on consecutive days.

Congo red should not be employed in the treatment of hemorrhages due to abortion, to an extrauterine pregnancy, to polyps, etc. It is conceivable that a substance which exerts its hemostatic effect could not possibly be employed for the treatment of the above-mentioned hemorrhages, that is, hemorrhages due to abortion, where the source of bleeding is a coarse anatomical lesion.

Kittner tested the menostatic effect of Congo red in a number of cases of functional organic injuries, without severe anatomical changes, responsible for the genital hemorrhage. In one group of cases Congo red was used although the hemorrhage was due to inoperable carcinoma of the cervix where the hemorrhage was either the first symptom of the affection or followed roentgen treatment. In some of these cases excellent results were obtained, although good results were not expected; *a check-up revealed that Congo red is an excellent therapeutic agent for the treatment of hemorrhage due to carcinoma.* Congo red is naturally ineffective in cases where the hemorrhage is due to erosion of a large vessel. In those cases, however, where the hemorrhage develops slowly, Congo red is definitely indicated. Of the 13 cases due to carcinoma of the cervix, one to three injections have controlled the hemorrhage in 12 cases.

Congo red was employed in 47 cases of genital hemorrhage due to inflammation. In most of these cases one had to deal with endometritis usually accompanying an acute or chronic recurrent inflammation of the adnexa; in some cases the endometritis was gonorrheal in nature. The hemorrhages appeared in the form of excessive menstruation and in some cases in the form of metrorrhagia. The Congo red was found especially valuable in the treatment of the cases which were hospitalized because of the hemorrhage. In 30 cases of gonorrhea with an involvement of the adnexa, the complicating hemorrhage was very favorably influenced by the Congo red injections, so that 23 cases were discharged as cured soon after the treatment was instituted, while in the remaining cases the treatment was somewhat more prolonged.

In summary, it may be stated on the basis of treatment of 71 cases that Congo red is especially effective in the treatment of genital hemorrhages of an inflammatory origin; in 78.7 per cent of these cases the hemorrhage was made to disappear after one to three injections. It is similarly effective in the treatment of hemorrhage due to carcinoma of the cervix. It is ineffective in the treatment of hemorrhage due to glandular hyperplasia. Nothing definite can be stated regarding its effectiveness in cases of juvenile hemorrhages. In none of the cases studied did Congo red give rise to unpleasant or undesirable side effects.

Nikolajew and Gurewitsch[36] confirmed the results obtained by Kittner. They stated that Congo red therapy gives very good results in adnexitis of inflammatory origin, arresting hemorrhage almost immediately after one to two injections. In nontoxic hemorrhage, the dye is ineffective. Deinhardt[13] and Rossak[39] likewise confirmed these findings.

Graves and Kickham[15] have had such satisfactory experiences with Congo red for the control of bleeding that they wish to call attention to its value as a hemostatic agent. They state:

> During the past two years, we have had such satisfactory experience with Congo Red for the control of bleeding that we wish to call attention to its value as a hemostatic agent, in cases of active hemorrhage, where ordinary medical measures have failed. Its apparent usefulness

is in the control of hematuria, in cases of pyelonephritis, benign hypertrophy of prostatitis and severe epistaxis.

Five cubic centimeters intravenously constitutes the usual dose. There is no presence of Congo red in the urine after injection.

### RETICULO-ENDOTHELIAL SYSTEM AND RESISTANCE TO TRANSPLANTABLE TUMORS

An enormous amount of controversial literature has accumulated on the subject of immunity to transplantable tumors. Ten years ago Woglom, analyzing the contents of more than six hundred papers on this subject, could not arrive at any definite conclusion. From that time on, the experiments with immunization against tumors have been going on, with little and doubtful success. These experimental observations indicate, however, that resistance to the growth of transplantable tumors can be increased by a previous tumor growth or by injection of such material as embryonic skin.

The presence in the skin of agents which inhibit the tumor growth has been demonstrated by a number of authors (Murphy, Besredka), although the inhibiting effect seems to be of temporary duration.

In spite of intensive investigations in this direction, it has not been possible to procure an immunity to tumors by the injection of an antitumor serum prepared along the same lines as antiserums for diseases of microbial origin or for agglutinin and the like (Colwell[12]). Moreover, attempts to prepare specific precipitins for neoplastic tissues have likewise failed.

The study of protective mechanism against the tumor growth reveals that this mechanism depends in some form or other upon the reticulo-endothelial system. *There seems to be a general agreement on this subject,* still the exact nature of this protective mechanism is not yet sufficiently understood. Some recent data might give indication, however. Thus Ludford,[24] studying the reaction in tumors following the inoculation of embryo skin (as well as of tumor cells previously killed), has reached the following conclusions: (1) lymphocytes appear in large numbers around the site of inoculation during the development of immunity; (2) killed tissues produce no immunity and no lymphocyte infiltration; (3) when small groups of lymphocytes occur in tumors which are growing well, they are only found in areas of spontaneous healing.

These observations corroborate those of Murphy and his coworkers at the Rockefeller Institute.[33,34,35] Applying a small dose of roentgen radiation previously to graft, thereby producing lymphocytosis, Murphy and his coworkers could considerably increase the resistance of animals towards transplanted tumors (also Sokoloff[44]).

The state of overactivity of the reticulo-endothelial system associated with lymphocytosis seems to be unfavorable to tumor growth. Sokoloff,[42,43] studying the macrophagic reaction in the case of grafted tumor, has pointed out that the polyblasts (the enlarged lymphocytes—according to Maximow's terminology) and macrophages seem to play an active rôle in the protective mechanism against tumor growth. According to Sokoloff, the immunity against tumor depends on histiocyte reaction, which can be observed in different organs of the animal. When the histiocyte reaction is more intense and of longer duration, the resistance to tumor growth seems to be more pronounced. Volterra[48] believes in direct relation between the immunity and the state of the reticulo-endothelial system. In his opinion, necrohormones of Caspari produced by tumorous cells are stored in histiocyte cells, and, if the quantity of necrohormones is large enough, there is observed a paralysis of the histiocyte activity.

The experiments of Zacherl,[53] Brüda,[7] Ludford,[24] Mottram and Russ,[32] and others, permitted the conclusion that if the reticulo-endothelial system is depressed by heavy doses of roentgen radiation or blocked by massive doses of vital electronegative dye, the resistance to transplant-

able tumors can be broken almost completely. Thus, there seems to be some similarity in the effect of roentgen rays and vital dyes upon the activity of the reticulo-endothelial system. *Small doses of electronegative dye have a stimulating effect whereas massive doses produce a depressing effect.*

In all probability, there exists a number of substances which, according to the quantity applied, may act as stimulants or depressives to the reticulo-endothelial system, and therefore as inhibitors or stimulants of transplantable tumors. This fact, which is of prime importance, should not be overlooked. It might explain the existing contradiction and controversy in the literature, as far as this subject is concerned.

### CONGO RED AND RESISTANCE TO TRANSPLANTABLE TUMORS

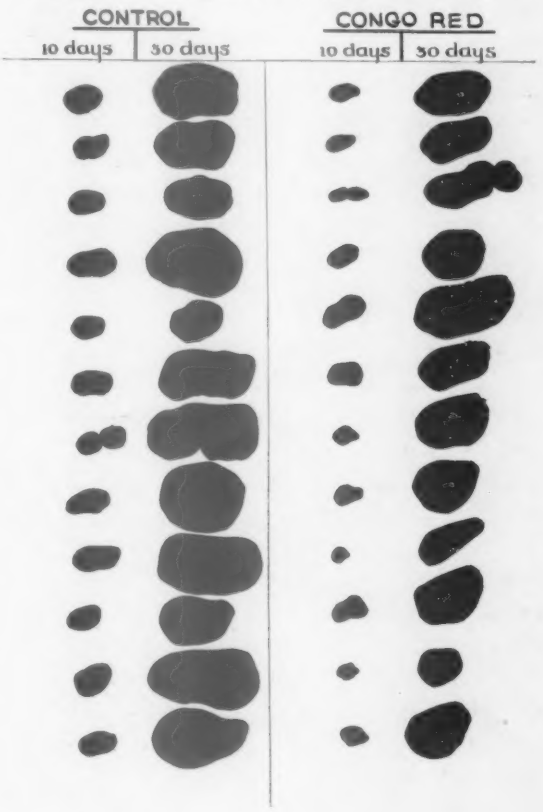
Considering the already established fact that Congo red in small doses has a stimulating and probably stabilizing effect on the reticulo-endothelial system, we decided to study the influence of this dye on the growth of transplanted mouse sarcoma 180 We conducted these experiments in two directions. In one series of experiments, the tumor was transplanted subcutaneously, as usual. In the other series, the transplantation was performed intracutaneously.

Two injections of Congo red (0.10 of 1 per cent solution) was given intraperitoneally, as soon as the beginning of tumor growth was noted. As a rule, we grafted very small pieces of tumor. The tumor was measured every five or six days. Our experiments were performed on a total of 192 animals.

Table I presents our series of experiments with subcutaneous transplantation, the experimental animals receiving two Congo red injections, the control not receiving any.

From the analysis of Table I we may conclude that Congo red injected intraperitoneally, in very small doses, slightly inhibits the growth of subcutaneously transplanted mouse sarcoma 180. After thirty days, the average tumor of the mice in this series which received Congo red had a surface dimension of 2.8 sq. cm.; the tumors of the control mice averaged 4.1 sq. cm. In the other series of experiments, this inhibition was less pronounced. Thus in total, the average tumor (of the 48 animals which received Congo red) was

TABLE I *Subcutaneous* S. 180

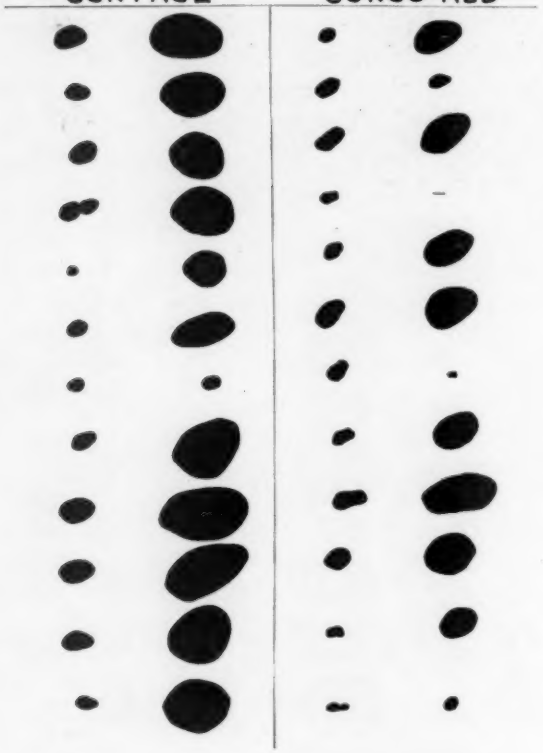



3.2 sq. cm. as against 4.0 sq. cm. for the control mice (see Table III, left side).

Table II presents a series of experiments with intracutaneous transplantation. The tumor, sarcoma 180, was grafted intraskin. This way of grafting has reflected on the growth of the transplanted tumor.

We may mention that growth of the tumor was slower in the beginning. However, in the majority of cases, the tumor has reached the same dimensions as subcutaneous graft by the end of the experiment. The inhibiting effect of Congo red, on the other hand, seemed to be more pronounced in this series. There has been a

TABLE II *Intracutaneous* S 180




considerable number of resorbed tumors. Thus, among the 48 control animals, on whom the graft was performed intracutaneously, 8 of the tumors (or 15 per cent) regressed and gradually disappeared. The incidence of tumor resorption was even greater in the series of these experiments in which Congo red was administered. Among the 48 experimental animals, in 12 cases (or 25 per cent) the tumors were resorbed. In total, the surface dimensions of the average tumor of the 36 experimental animals was 2.7 sq. cm. (with Congo red) and 4.1 sq. cm. (of controls) (see Table III, right side).

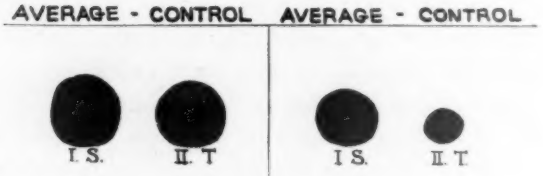
Summarizing the results of our experiments of the second series, we may say that Congo red injections have a more inhibiting effect on tumor growth when the tumor has been grafted intracutaneously.

In our next series of experiments, we reinoculated the animals whose tumors had been resorbed. Four weeks after the first graft disappeared, they were re-inoculated with sarcoma 180. This time, larger pieces of tumor were transplanted. All of these animals, with the exception of 2, showed a complete immunization against sarcoma 180. In 2 cases, the tumor grew very slowly, reaching a dimension of about 0.75 cm. in diameter. The animals were killed and the tumors examined. The tumor tissue showed a state of pronounced disintegration, associated with lymphocyte invasion.

In this immunity against transplantable tumor, two factors might be responsible: previous inoculation of a small piece of tumor intra skin, and Congo red injection. Nevertheless, this combination of two factors, each of which might be considered as having a stimulating effect upon the reticulo-endothelial system, has proved to be more effective.

Indirectly, our experiments gave support to a recent observation of Besredka. He and his associates called attention to the active

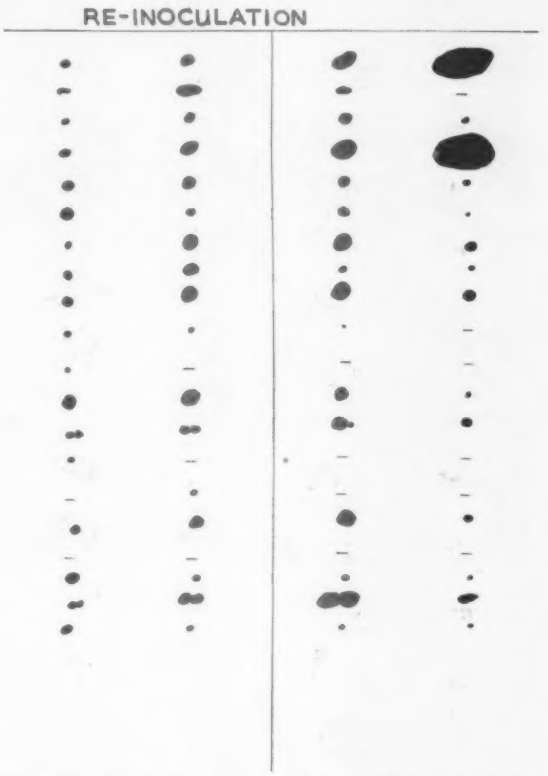
TABLE III



rôle which the skin seems to play in immunization against transplanted tumors. According to his observation, intracutaneous injection of the Pearce-Brown rabbit carcinoma is followed by the appearance of a tumor which, after about three weeks, may regress entirely. The animal is then resistant to re-inoculation and continues thus for at least ten months (Besredka[9,10]).

Besredka demonstrated that the intracutaneous injection of either embryo or normal adult tissue, or even of inactivated tumor tissue, is not attended by any such response. He claims that the skin offers a much greater resistance to tumor growth and once the intracutaneous graft is resorbed, the animals obtain thereby a definite immunity against the same type of tumor. To Besredka, *this immunity appears to be cellular*. In other words, it does not depend upon an elaboration of antibodies in the blood serum, but as in anthrax, it is induced by a local vaccination of the skin and through the lymphatic apparatus. Besredka's theory does not seem to be without grounds. There are many indications that resistance to malignancy depends on factors which are unlike those on which resistance to infection is based. Cellular dynamics has its own law of regulation and, in all probability, the decisive factor in immunity against malignancy is some specific elements of the reticulo-endothelial system belonging to the organism which controls the cellular dynamics—endocrine glands.

TABLE IV *Subcutaneous* S. 180




### RETICULO-ENDOTHELIAL SYSTEM OF ADRENALS AND CANCER

We have already pointed out that there seems to be a general agreement that immunity against malignant disease depends on the state of the reticulo-endothelial system. But studying the activity of the reticulo-endothelial elements, the majority of authors have almost completely neglected the rôle which the reticular tissue of endocrine glands (particularly that of adrenal glands) may play. This last question, however, acquires particular interest, considering the fact that the adrenals are an important source of some of the body lipoids. The fact is known that 33.6 per cent of the human adrenals consists of an ether soluble substance, 20.6 per cent of which is cholesterol. The importance of the lipins in the various processes of immunity is generally recognized. Therefore, *a priori* change in character of the lipoid element of the adrenal cortex, which is observed under the influence of various substances, might be of some importance. However, these changes which are observed in adrenal cortex often have no specific significance. Thus, hyperepinephry might be manifest under many conditions outside of the influence of carcinogenic factors and might vary in intensity. As a rule, it is characterized by exaggeration of the adipogenic function of this organ and by spongiocytic transformation of the cortical cells. It is accompanied by considerable elaboration of pigment and is sometimes associated with medullar hyperactivity and hyperplasia.

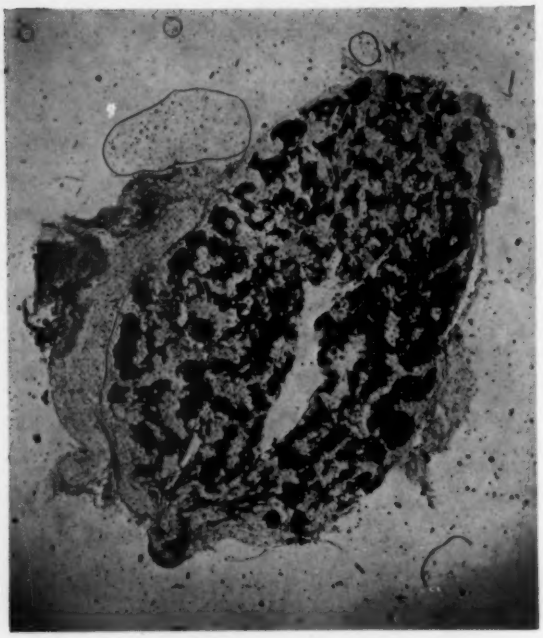


FIG. 1. Chicken adrenal cortex. Normal. Sudan ×15.

According to Parisot, there is no clearly defined distinction between the initial inflammatory lesion and simple physiological hyperactivity of the gland, and the variation in the physiochemistry and histology of the adrenal gland is nothing but a reflection of its unusual sensitivity to every even slightly toxic substance. This fact is often underestimated by workers, who are inclined to attribute too much importance to deviation in histology of adrenal which they may observe. Nevertheless, under carcinogenic substance, as well as in malignancy, there can be observed very significant modifications in the reticulo-endothelial system of the adrenals.

A few years ago, one of us (Sokoloff[45]) observed that chicken bearers of the Rous sarcoma often have unusually large adrenal glands. About 40 chickens were examined and the histology of their adrenals was studied. The weight of the adrenal in a normal chicken is about 100 mg. As soon as the grafted tumor begins to grow, the weight of the adrenal is between 175 and 200 mg. A chicken whose tumor is very large may have an adrenal weighing 400 mg. Histologically, the adrenals do not show any metastasis. This is merely a physiological reaction of the adrenal to the growth of the tumor. The cortical part of the gland reacts the most. At the beginning of tumor growth, only a slight hyperactivity of spongiocytes can be observed, which is translated by alteration of the mitochondria. An increase in the number of mitoses and a decrease of the lipoid vacuoles may be noted. With a large tumor affecting the chicken, an adiposis of the entire cortical part is observed. The slides stained with Sudan III show a picture of fatty degeneration and hypertrophy of the gland (Figs. 1 to 6). Mouse sarcoma 180 or the Bashford mouse sarcoma produced less intense reaction of the adrenals.

Examination of Altmann's granules shows that the first reaction, which can be observed after the beginning of growth of sarcoma 180 consists in augmentation of the number of these granules. This reaction may be observed in the X-zone of the reticularis (Fig. 8). This slight activity of the reticular zone is associated with the disappearance of the lipoid granules from

FIG. 2. Rous sarcoma. Chicken adrenal. Sudan ×15.

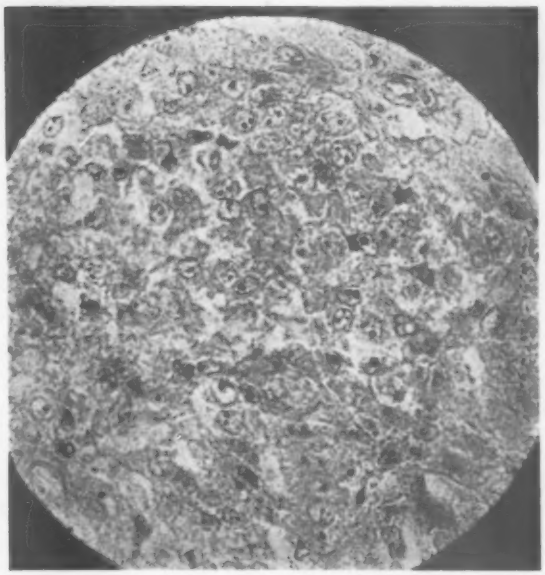


Fig. 3. Rous chicken sarcoma. Showing changes in adrenal cortex.

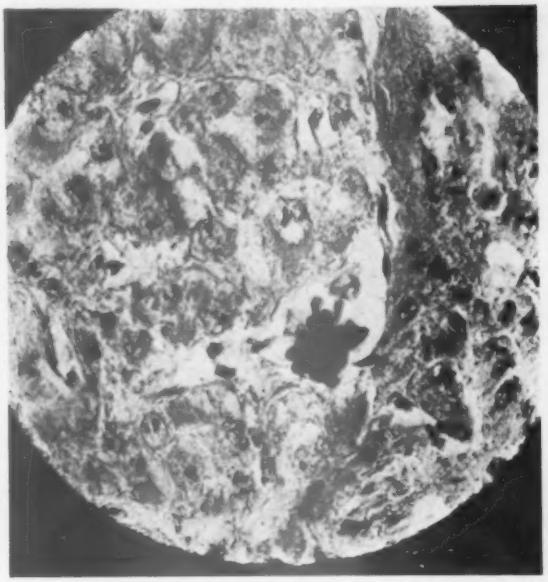


Fig. 5. Rous chicken sarcoma. Showing changes in adrenal cortex.

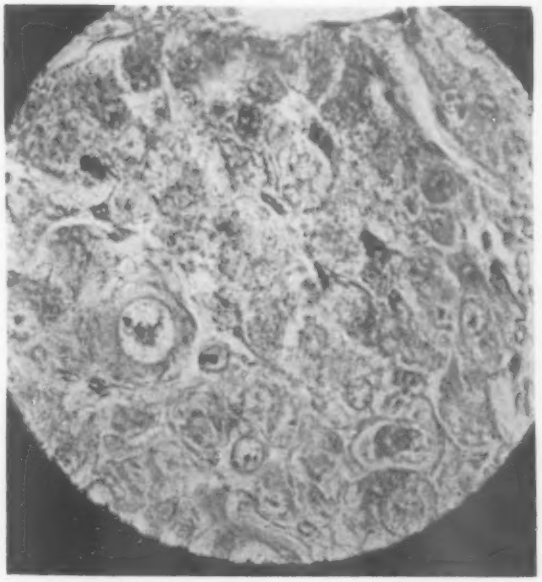


Fig. 4. Rous chicken sarcoma. Showing changes in adrenal cortex.

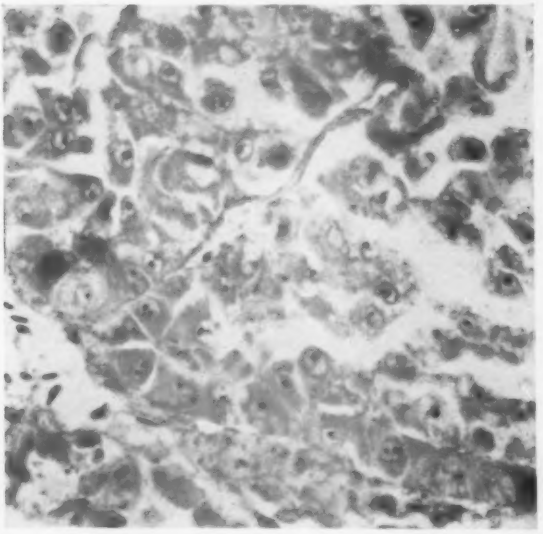


Fig. 6. Rous chicken sarcoma. Showing changes in adrenal cortex.

the fascicular zone.* The second stage is that of augmentation of lipoid formation. The Altmann granules have a tendency to disappear gradually and it is then often difficult to detect their presence.

We find in the adrenal cortex two types of reticulo-endothelial cells. In the smallest cells, the nucleus shows an intense chromatin stain, while the cytoplasm consists of a very small amount of basophilic material, staining blue with methyl green

* Max Aron observed similar changes in the adrenal cortex after injection of the concentrated urine from a cancer patient. We must admit that the instability and variety of cytological changes of the fascicular zone offer considerable difficulty, as far as the diagnosis of malignant disease is concerned.

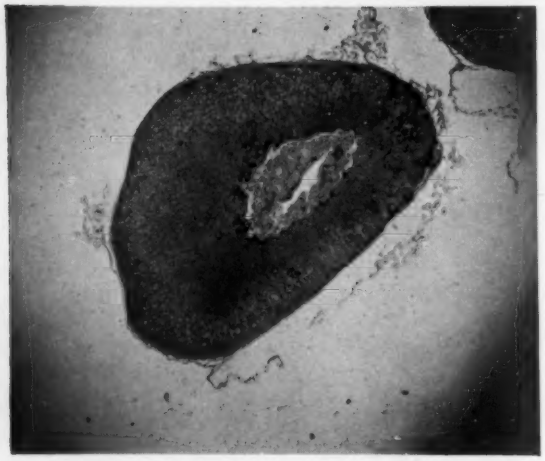


FIG. 7. Normal mouse adrenal.

pyronine. Sometimes these large cells contain fatty vacuoles. This type of cell resembles the macrophage. With growth of the tumor, there may be observed an augmentation in the number of these large reticulo-endothelial cells. Some of them even invade the external part of the medulla. When the tumor is ulcerated and of considerable size, these cells disappear more or less completely from the reticular zone. Instead, the small cells increase in number. They may be observed in the fascicular zone as well as in the reticular zone. There can be observed in the adrenal cortex also a large myeloid infiltration (in the case of an ulcerated tumor).

There is some similarity between the reaction of the adrenal towards the growth of mouse sarcoma and the reaction which can be observed in this gland as a result of continuous injection of estrin. Our experiments included 6 male mice of pure line which received estrin subcutaneously for several months.*

*Technique.* Young mice, eight weeks old, were injected with 0.02 per cent of estrin twice a week. The animals were killed after twenty, thirty and thirty-five injections and their adrenals examined. Not one of these mice had developed a breast tumor.

The first reaction which could be observed was hyperplasia of the X-zone of the reticularis. Cellular pigment was increased in volume. A few mitoses could be observed in the fascicular zone in the area near the reticular zone. Later, symptoms of cellular degeneration appeared especially in the reticular zone. Vacuolization of protoplasm was accompanied by an accumulation of pigment in the cells of the reticularis. The cellular incorporations lost their regular character. The number of mitoses in the fascicular zone was slightly increased, although only a few of them could be observed. Some activity in the medulla was noted. However, the principal change was manifested in the cortex. The picture of the adrenals, after the animals had received twenty to twenty-five injections of estrin, was one of reticular hyperplasia and hyperepinephry with cellular disintegration.

Our description of these changes, resulting from the application of a large dose of estrin, corresponds to that given by Burrow, Cramer and Horning. According to our observations, however, the initial state of hyperplasia originated in the X-zone of the reticularis. According to Lacassagne[21]

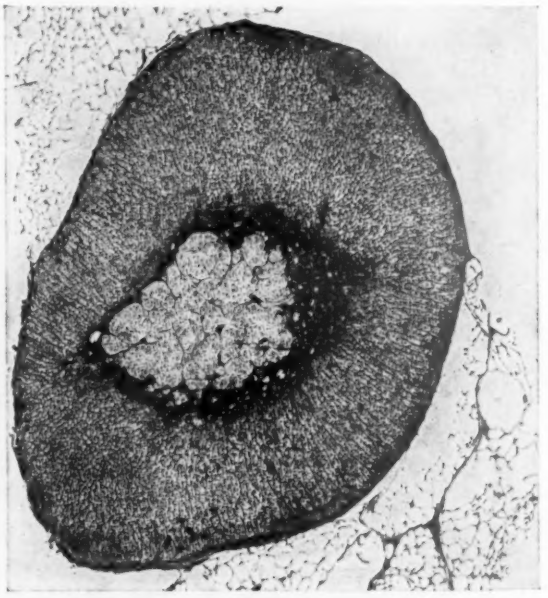


FIG. 8. Sarcoma 180. Changes in adrenal of mouse.

* We thank Dr. Leo Loeb for his kind cooperation in supplying these mice. According to him, the incidence of breast tumor among the females of this line is about 50 per cent.

the X-zone of the cortex might disappear under prolonged massive doses of estrin, if the injections were started a few days after birth.

Regarding our observations we may say that the reticulo-endothelial cells of the adrenals respond very soon to the growth of tumor, as well as to a massive dose of carcinogenic substance, such as estrin.

The effect of Congo red on the reticulo-endothelial cells of the adrenal has been investigated by us.

Congo red, if introduced directly into the adrenals, is deposited in the reticular zone. It is soon eliminated, producing a stimulating effect on the reticular cells. This effect may be interpreted in the sense that the mitochondrial cellular apparatus shows an increase in activity, without any sign of degeneration. The small granules still have a typical semicircular form, but they are more numerous (Fig. 9). The activity of the reticular zone seems to have some reflection on the fascicular zone, the number of lipoid granules of spongiocytes being decreased. No increase of mitoses could be detected. The intraperitoneal injection of Congo red has a much less pronounced effect on the adrenal. A small dose, as a matter of fact, produces only a slight activity of the large reticular cells, without any visible change in the fascicular zone.

We were unable to find any toxic effect of Congo red on the adrenals, even when the dye was introduced in considerable amount.

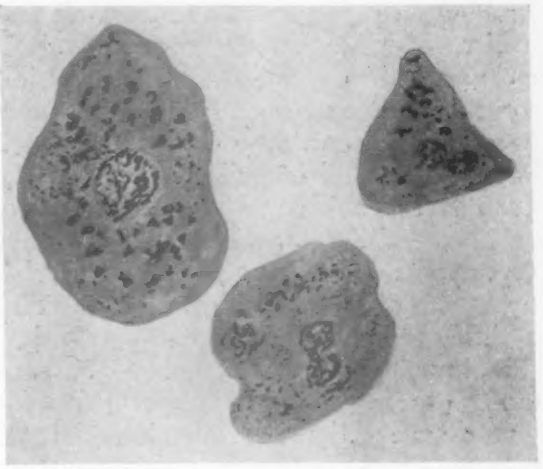


Fig. 9. Hyperactivity of reticular cells of cortex after Congo red injection.

### ROENTGEN SICKNESS AND ANEMIA

The rôle which the reticulo-endothelial system plays in resistance against malignant disease might suggest to the radiotherapist to take under serious consideration the possible effect which the irradiation might have upon the reticulo-endothelial system. There exists unquestionable danger that under heavy doses of roentgen rays the general resistance of the reticulo-endothelial system might be considerably decreased and therefore the door to generalized malignancy might be opened.

The radiotherapist is also often handicapped in his work by the general condition of the patient, especially when the malignant disease has reached an advanced stage. Large doses of roentgen radiation often produce an undesirable effect on such patients. The radiotherapist has at his disposition neither a method nor a remedy to combat the aftereffect of irradiation. Quite frequently it has become necessary to bring the treatment to a close because of the patient's alarming condition, characterized by hemorrhages or pronounced anemia. We need not repeat that the general condition of the patient is an important factor in the fight against malignancy, since malignancy cannot be regarded as a purely local condition. In this respect, roentgen sickness—nausea, vomiting—is one of the most usual manifestations of this disturbance. Roentgen sickness, which was first described by Gauss, can be produced experimentally in animals, according to Maruyama.[25] Irradiation at definite intervals evokes an anaphylactic or allergic reaction in guinea pigs, corresponding to roentgen sickness. Several theories have been expressed in an endeavor to explain the underlying causes of this sickness. Schreus and Willms[41] attributed these manifestations to an increase of beta-oxybutyric acid in the blood, as a result of

irradiation. Hug[17] is inclined to think that a disturbance in metabolism, particularly a change in blood cholesterin, is responsible for this sickness. Jugenburg, Peretz and Mostowa[19] claim that roentgen sickness is due to a lack of balance in the bacterial flora of the colon and the resorption of products of decomposition. Others have expressed the opinion that the vegetative nervous system may play an important rôle. However, the so-called roentgen sickness, in reality, is but one symptom among many others which are a reflection of a disturbance of the reticulo-endothelial system observed during and after roentgen irradiation.

Several attempts have been made to treat roentgen sickness but with only partial success. Insulin and liver extract have been suggested. Webster[50] and Young[52] reported satisfactory results from liver therapy; in 53 per cent of the cases treated, the patients obtained considerable relief from these symptoms.

During the last three years, we have often given injections of liver extract to our patients during roentgen treatment. In some cases, the general condition was improved and the symptoms of roentgen sickness considerably decreased. But often, liver therapy was not sufficiently effective and this was especially true in cases of roentgen hemorrhage.

Our laboratory experiments with Congo red have convinced us that this mono-azo dye might be of practical value in radiotherapy. Its hemostatic effect, its antihemolytic properties and its harmlessness justified the use of Congo red in general medical practice. The fact that this dye has some inhibiting effect on the growth of transplanted tumors and a stabilizing action on reticulo-endothelial cells, suggests its application in radiotherapy. The results of our clinical observations, in this last respect, have been encouraging.

*Technique.* The patients received three injections of 5 cc. each of 1 per cent isotonic solution of Congo red.* We never observed any painful reaction or increase in temperature. The blood of the patients was examined several times, during and after treatment.

Summarizing briefly the results of Congo red therapy, which was applied to 70 patients receiving roentgen irradiation, we may state:

The polynucleosis which is, as a rule, observed in malignant disease and which is often increased by roentgen irradiation, was completely controlled in the majority of cases by this therapy. The number of polymorphonuclear leukocytes was decreased from 85 to 90 per cent down to the normal level. Lymphopenia, observed in almost every second case of malignant disease, was corrected. The number of monocytes was doubled in some cases and slightly increased in others. The reticulocytosis consistently followed the Congo red injection, but a few days later the number of reticulocytes returned to normal. Generally, the blood picture was considerably improved even in advanced cases of malignant disease treated by us. Hemorrhages were often arrested after two or three injections of Congo red. In a few cases, however, they could not be controlled. It seems that Congo red is effective only in hemorrhagic diathesis. The patients were relieved of the symptoms of roentgen sickness, except two cases of advanced carcinoma of the stomach.

## SUMMARY AND CONCLUSIONS

The resistance against transplantable tumors, as well as against malignant disease in general, depends on the state of the reticulo-endothelial system. By blocking this system, the resistance might be broken down. The reticulo-endothelial system may be stimulated by means of small doses of roentgen radiation, or by a small dosage of electronegative vital dye, such as Congo red.

It was furthermore demonstrated that Congo red seems to be a powerful hemostatic agent, which property is due to its specific action upon the cells of the reticulo-

* We have been using B. E. form of Congo red.

endothelial system. In toxic hemorrhage, Congo red, intravenously injected, may stop the bleeding almost immediately. Its practical value in radiotherapy has been discussed. An analysis of seventy patients, treated with Congo red, suggests its application in roentgen sickness and anemia.

The reticulo-endothelial system of the adrenals has been studied. It was noted that the X-zone of the reticularis reacts to growth of transplanted tumors, as well as to the injection of estrin.

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# CASE REPORT FROM THE WEEKLY SEMINAR OF THE DEPARTMENT OF ROENTGENOLOGY, MASSACHUSETTS GENERAL HOSPITAL

*Prepared by* J. R. LINGLEY, M.D.
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CASE 145385. A sixty-four year old American male entered the hospital because of swelling of the left thigh of fifteen months' duration.

The swelling appeared without antecedent trauma and, when first noticed, it was about 1 or 2 inches in diameter. It grew very slowly during the first two months, but later it increased in size rapidly until, on admission, it had reached the size of a football and occupied the soft tissues of the entire anterior thigh. A nagging ache in the thigh and knee developed nine months previously, increasing in severity. During the past two months he had lost 15 to 20 pounds in weight.

Physical examination revealed an emaciated, elderly man in no acute distress. There was a fusiform, hard, non-tender swelling of the whole of the left anterior thigh measuring 25 cm. long and 20 cm. in width. The superficial veins were dilated and there was some edema of the lower leg and ankle.

The blood showed a red cell count of 3,900,000 with 60 per cent hemoglobin. The white cell count was 6,400 with 80 per cent polymorphonuclear leukocytes. The Wassermann reaction was negative. The non-protein-nitrogen was 38 mg. per 100 cc.

An intravenous pyelogram revealed nothing abnormal in the kidneys or urinary passages.

Dr. Schatzki will discuss the films of the chest and left thigh.

DR. SCHATZKI: The film of the chest shows apical scars on both sides and arteriosclerosis of the aorta, but apparently nothing that has any bearing on the findings in the thigh. There is marked swelling of the soft tissues of the thigh, anterior to the femur (Fig. 1) but no evidence of swelling behind the bone. In the anteroposterior view, the swelling seems to be lateral, rather than medial, to the femur. In view of the finding of edema of the lower leg, it might be worth while to consider this as the cause of the swelling of the thigh. On analysis of the films, however, edema does not seem likely. The skin and subcutaneous tissue appear well defined and show no evidence of pathology aside from a fairly thick panniculus adiposus which the patient probably had before he became sick. The pathology lies below the fascia in the region of the muscle. The soft tissue swelling is fairly well defined by the fascia below the subcutaneous tissue but it is not well delimited above and below. The outline of the mass close to the surface of the bone is very irregular and there is no definite evidence of involvement of bone. The soft tissue mass itself is not homogeneous. It consists of band-like and round areas of decreased density with fairly similar areas of normal soft tissue. There is no calcification within the mass.

FIG. 1. Lateral view of the thigh showing the large, soft tissue tumor. Note the heterogeneous nature of the tumor, due to the presence of multiple, large, radiolucent areas within it.

FIG. 2. Reproduction from the same roentgenogram as Figure 1, but with greater exposure and more contrast to show the radiolucent areas in the tumor.

What can produce decreased density in the soft tissues? I know only of two possibilities: (1) fat, (2) air. The history gives us no reason to suspect air. The areas are not sufficiently radiolucent to be due to air. The mass must therefore be a mixture of two substances: a fatty material and some other soft tissue.

The most common soft tissue tumors, fibroma and fibrosarcoma, can be excluded on account of the heterogeneous soft tissue shadow. Could it be a myxosarcoma? Mucus in a sarcoma gives the same density as water, and therefore the same density as normal tissues.

Could it be a hemangioma with a great deal of fat? The usual cavernous hemangiomas are solid tumors due to large blood chambers. The arterial racemose hemangioma is the only vascular tumor that could conceivably produce such a picture, assuming the vessels to be surrounded by fat. However, such a large amount of fat in a hemangioma is unlikely and the soft tissue of the tumor does not appear to be composed of blood vessels. Was there any bruit over it?

DR. LINGLEY: No mention is made of a bruit. The record states, however, that the mass did not pulsate.

DR. SCHATZKI: Could it be just a lipoma? A lipoma is much more homogeneous. It consists of large globules of fat and it is well defined.

Could the unequal densities in the mass be due to deposits of fat in necrotic areas of a fibrosarcoma or myxosarcoma? If this were the case, I would not expect the fat to be deposited in such large masses. I cannot definitely rule out this possibility, however.

I am left with two alternatives: The tumor is either a liposarcoma or we are dealing with fatty degeneration within some other kind of a tumor, such as fibrosarcoma or myosarcoma. In either case, I think it is a malignant tumor of the soft tissues. Further, I believe that liposarcoma, a malignant tumor of the soft tissues containing large areas of radiolucent fat, should produce just such an appearance and that it is the most likely possibility.

FIG. 3. Roentgenogram of the specimen after removal and formalin fixation.

Dr. McPeak: If the areas of rarefaction were due to necrotic areas in the soft tissue, would the tumor not show a diffuse mottling?

Dr. Schatzki: Broken down soft tissue, unless it contains fat, produces the same density as normal tissue. Therefore, the tumor must contain fat. I at first excluded fibrosarcoma. While discussing the case, however, and describing the details of this mass, the idea occurred to me that it might be a broken down tumor with fatty deposits within necrotic areas. I still consider this as a possibility but not a likely one.

Dr. Lingley: Do you wish to make a diagnosis, Dr. McPeak?

Dr. McPeak: I would favor fibrosarcoma.

Dr. Schatzki: If you consider the possibility of broken down tumor, it could be any one of a number of malignant necrotic tumors which appear in soft tissue.

Clinical diagnosis: Sarcoma
Dr. Schatzki's diagnosis: Liposarcoma
Pathological diagnosis: Liposarcoma

Dr. Castleman: The most common tumor in this region of the leg is the myxofibrosarcoma. This tumor, however, was not that. A hip joint disarticulation was performed. The tumor, except for its extreme proximal tip was encapsulated and measured 25×15×13 cm. Upon section it was soft yellowish white and had the consistency of brain tissue. Some parts were very white, soft and granular and others definitely necrotic. Histologically it was a definite liposarcoma, the second case that we have seen here, the other being in the popliteal space. The cells were very large, polyhedral, with foamy cytoplasm that takes the fat stain. In other areas there were embryonic fat and tumor giant cells. Throughout the tumor all stages of fat cells from small embryonic fat cells to large adult fat cells could be found, a fact that definitely rules out fatty degeneration of fibrosarcoma, a condition that is sometimes erroneously called a liposarcoma histologically.

Dr. Hampton: The patient was referred to us following amputation for roentgen therapy with the note that this was the seventy-second case of liposarcoma reported in the literature. I had never heard of one being treated by irradiation. Since then we have discovered a number of reports in the literature of cases that have been treated, some with and some without success. No roentgen treatment was advised in this case.

Fig. 4. Photograph of the specimen, bisected in its long axis.

Dr. Schatzki: Do they recur locally or metastasize?

Dr. Castleman: Both—although recurrences are more common.

Dr. Schatzki: How can we differentiate a liposarcoma from other necrotic, fat-containing tumors on the roentgenogram?

Dr. Castleman: Histologically, in a true liposarcoma, one should see all stages of development of the fat cell, in contrast to more focal fatty changes in other tumors. Grossly, in the latter, there are no large fat-containing areas such as are found in a liposarcoma. There should, therefore, be no chance to confuse them in the roentgenogram.

## BRIEF REVIEW OF LITERATURE ON LIPOSARCOMA

Virchow[11] in 1857 reported the first accurate histopathological study of this type of tumor. A review of the literature reveals that it is a rare tumor, occurring with equal frequency in the two sexes in adult life. Although many sites of origin have been reported, the most frequent location is in the soft tissues of the lower extremity. In a series of 12 cases reported by Geschickter,[3] 5 were in the thigh or lower leg; and in a series of 51 cases collected from the literature by Robertson,[6] 42 per cent were in the

lower limb or buttock. The retroperitoneal region is second in frequency as a site of origin, von Wahlendorf[12] reporting a large series found in this region. Stewart[10] reported 3 probable cases which were primary in bone marrow.

The symptoms and clinical course of liposarcoma are those of a mass which may exhibit a slow rate of growth at first, even over a period of two or three years. Ultimately, growth becomes more rapid and normal function of the surrounding parts is impaired by compression from the growing tumor. Pain is usually not a prominent feature but may occur from pressure or hemorrhage. Weakness, anorexia, and loss of weight and strength are observed after growth is well advanced. Hirsch and Wells[5] reported a case of retroperitoneal liposarcoma in which the tumor weighed 69 pounds. Seids and McGinnis[7] report that John Delamater in 1859 described a remarkable fatty tumor that weighed 275 pounds. This tumor developed retroperitoneally and a portion extended through the pelvis to form a perineal tumor 4 feet in diameter. The circumference of the abdomen was 7 feet 8 inches.

The histopathology of liposarcoma is described by Ewing,[1] Shaw,[9] Geschickter,[3] Robertson,[6] Seids and McGinnis,[7] and others. Geschickter, in a short summary states: "Liposarcoma shows extremely variable microscopic features. The predominant malignant tissue either resembles a fascial sarcoma with compact spindle cells, or shows numerous immense tumor giant cells with degenerating nuclei and a large amount of foamy cytoplasm. Surrounding these malignant areas are islands of embryonic fat, adult fat, and myxomatous like stroma. A small cell resembling a plasma cell is often seen."

All authors are agreed on the marked degree of malignancy of this tumor. The mass is usually encapsulated and, if simply shelled out or excised, it invariably recurs locally. Even fairly wide excision may be followed by local recurrence and metastasis. In Geschickter's series of 12 cases the tumor recurred after excision in every case but one which was only recently observed. No case was reported cured.

Reports on the radiosensitivity of this tumor vary greatly. Geschickter reported rapid decrease in the size of the local growth in the 4 cases in his series that were treated but ultimate death from metastasis. Stewart[10] reported a case in which pulmonary metastasis was treated and remained under control for five years, the patient then dying of cerebral metastasis. He also reported a far advanced case with multiple bone involvement in which the bone lesions reacted favorably to irradiation. Fender[2] reported a case of cerebral metastasis in which the patient appeared to be benefited by irradiation. Seids and McGinnis state: "Roentgen therapy with improved technique may prove beneficial as it did in one of our cases. However, it was used intensively in three other cases with no avail." Ewing states that liposarcomata are notably resistant to irradiation.

The opportunity of making a roentgen diagnosis of liposarcoma occurs rarely. Since this tumor contains large areas of radiolucent fat, irregularly distributed throughout tissue of greater density, the roentgenogram should furnish a valuable clue to the nature of the tumor. The roentgen diagnosis not only appears to be possible when the lesion occurs in an extremity but would seem to be the only logical result of a careful analysis of the composition of the tumor mass.

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# EDITORIAL

## SPONTANEOUS MEDIASTINAL EMPHYSEMA

HAMMAN,[1] in the Henry Sewall Lecture in Medicine, has dramatically called our attention to the not infrequent occurrence of spontaneous mediastinal emphysema and that unless the clinician keeps such a condition in mind it will escape diagnosis completely. This is owing to the fact that there are no constitutional symptoms, no evidence of shock and the temperature and pulse and respiratory rates as well as the blood pressure and the leukocyte count are very little, if any, altered, and that the only distinctive clinical sign of mediastinal emphysema is the peculiar sound heard over the heart with each contraction due, no doubt, to the air-filled mediastinal tissues which lie between the heart and the anterior wall of the chest. Hamman calls attention to the peculiarity of this sound which is quite different from any other heard over the heart area. It has been referred to by various observers as a crunching, bubbling, crepitant, crackling, clicking, popping sound and, no matter what the descriptive term is, once the sound is heard, its nature could scarcely again cause confusion.

The symptomatology in many of the cases is fairly similar. There is usually a feeling of sudden pressure under the sternum with not infrequently crackling sounds in the region of the heart which may attract the patient's attention. These crackling sounds usually occur synchronously with the heart beat, and, with change in the position of the patient, the sound in the region of the heart may completely disappear owing to the displacement of the air away from the cardiac area.

The mechanism of the occurrence of mediastinal emphysema is somewhat variable. Clinical observations demonstrate clearly that the pulmonary alveoli of healthy persons may rupture and allow air to escape into the surrounding connective tissue when there has been no trauma to the chest and no effort which might raise abnormally the intrapulmonary pressure. Hamman states that the symptoms usually come on abruptly, in some patients without any apparent warning, and he further says that circumstances justify the use of the term "spontaneous" even though it may be questioned whether normal alveolar walls can be ruptured so easily. It is conceivable, Hamman says, that the alveolar wall here and there may become attenuated and weakened, but how and why this should occur he does not know. Certain it is that alveoli may rupture even when they show no gross evidence of disease. Once the rupture has occurred, the escaped air infiltrates the surrounding tissue and travels along the fascial planes toward the mediastinum or the visceral pleura. Macklin, in some ingenious experiments, has demonstrated that in cats whose lungs have been ruptured by forceful distention the air travels toward the mediastinum along the sheaths of the arteries, and often there are continuous channels from the peripheral alveoli to the hilum.

The air, after having reached the hilum, spreads out in the mediastinum, collecting in bubbles along the borders of the mediastinum and about the blood vessels, infiltrating the tissues that lie between the heart and anterior chest wall. It is this distention of the mediastinal tissues that causes the pain, often of an extreme degree, which may radiate to the shoulder and down the left arm simulating the pain of angina pectoris. There may at times be an alarming feeling of distention or pressure

[1] Hamman, L. Spontaneous medastinal emphysema. *Bull. Johns Hopkins Hosp.*, Jan., 1939, *64*, 1–21.

under the sternum; at other times pain on deep breathing, on swallowing and with movements such as turning the head, which pull upon or distort the mediastinal tissues.

Once the air has entered the mediastinum, it may remain trapped and gradually be absorbed, or it may burrow along the fascial planes and appear at the jugulum and above the clavicles, spreading up the neck and over the front of the chest. Again it may follow the course of the aorta and esophagus, pierce the diaphragm at the crus, and infiltrate the retroperitoneal tissues. It is well known that retroperitoneal emphysema often follows traumatic mediastinal emphysema, and it has been observed that air injected into the intraperitoneal cavity has entered the mediastinum.

Mediastinal emphysema may be accompanied by pneumothorax, and there is experimental evidence to prove that pneumothorax, which often accompanies mediastinal emphysema, is produced by an escape of air from the mediastinum. The escaped air may travel along the interstitial bands of the lung to the pleura and form a subpleural bleb which may rupture. Hamman suggests, however, that it has never been demonstrated that this actually occurs and it seems altogether likely that in most instances, if not in all, the air reaches the pleural cavity through the mediastinum, and that some of the obscure cases of spontaneous pneumothorax may be secondary to a primary mediastinal emphysema.

Hamman emphasizes the fact that there is nothing new about the occurrence of interstitial emphysema of the lungs and mediastinal emphysema for they have been observed for hundreds of years, Laennec having given the first accurate description of the pathologic anatomy. But long before his time physicians had recognized the occurrence of interstitial emphysema of the lung by noticing subcutaneous emphysema about the neck after trauma to the chest and after distention of the lungs by violent effort when the glottis is closed. It has been observed in newborn infants after attempts at resuscitation; in children after severe paroxysms of coughing or crying, in pneumonia and bronchial asthma. Apparently heretofore the diagnosis of mediastinal emphysema was made only when air appeared in the subcutaneous tissues of the neck and Hamman thinks that this is somewhat surprising since the symptoms are distressing and the physical signs, when once understood, are clear in their implications.

The roentgenogram is an invaluable aid in establishing the diagnosis. Often when the characteristic sound over the heart is absent, the roentgenographic evidence of air in the mediastinum may be decisive, and it is important that in addition to the usual roentgenographic studies a lateral roentgenogram be made which will demonstrate the air between the heart and the anterior chest wall. But particularly is it important in the roentgenographic study to look for sharp and distinct lines running parallel to the borders of the heart, this line representing the outer wall of the mediastinum, though it must be borne in mind, as Arendt[2] has pointed out, that occasionally the normal mediastinal border is visible in adults, particularly on deep inspiration. The position of the border is quite variable. It may be seen as a vertical line close to the right border of the heart or as an oblique line along the left heart border, and in this latter case may produce a deformity of the heart shadow. It is of considerable importance not to confuse an accessory right lower lobe of the lung with a mediastinal border. Of course when the air reaches the subcutaneous tissues and neck and occurs above the clavicles the diagnosis is relatively easy.

The clear cut clinical description of mediastinal emphysema which Hamman has given, coupled with careful roentgenologic studies of the chest, should help to make possible a diagnosis of mediastinal emphysema before the occurrence of air in the tissues of the neck.

[2] Arendt, J. Zur Pathologie des Mediastinums. *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1933, *48*, 1–12.

# SOCIETY PROCEEDINGS, CORRESPONDENCE AND NEWS ITEMS

*Items for this section solicited promptly after the events to which they refer.*

## MEETINGS OF ROENTGEN SOCIETIES*

### UNITED STATES OF AMERICA

**AMERICAN ROENTGEN RAY SOCIETY**
*Secretary*, Dr. C. B. Peirce, Royal Victoria Hospital, Montreal, Canada. Annual Meeting: Chicago, Ill., Sept. 19–22, 1939.

**AMERICAN COLLEGE OF RADIOLOGY**
*Secretary*, Dr. E. P. Pendergrass, University Hospital, Philadelphia, Pa. Next Meeting: Jefferson Hotel, St. Louis, Mo., May 17, 1939.

**SECTION ON RADIOLOGY, AMERICAN MEDICAL ASSOCIATION**
*Secretary*, Dr. J. T. Murphy, 421 Michigan St., Toledo, Ohio. Annual meeting: St. Louis, Mo., May 15–19, 1939.

**RADIOLOGICAL SOCIETY OF NORTH AMERICA**
*Secretary*, Dr. D. S. Childs, 607 Medical Arts Bldg., Syracuse, N. Y. Annual meeting: Atlanta-Biltmore Hotel, Atlanta, Ga., Dec. 11–15, 1939.

**RADIOLOGICAL SECTION, BALTIMORE CITY MEDICAL SOCIETY**
*Secretary*, Dr. Walter L. Kilby, Baltimore. Meets third Tuesday each month, September to May.

**RADIOLOGICAL SECTION, CONNECTICUT MEDICAL SOCIETY**
*Secretary*, Dr. Max Climan, 242 Trumbull St., Hartford, Conn. Meets twice annually in May and September.

**SECTION ON RADIOLOGY, ILLINOIS STATE MEDICAL SOCIETY**
*Secretary*, Dr. W. W. Furey, 6844 Oglesby Ave., Chicago. Meets Rockford, Ill., May 2–4, 1939.

**RADIOLOGICAL SECTION, LOS ANGELES CO. MED. SOC.**
*Secretary*, Dr. Wilbur Bailey, 2007 Wilshire Blvd., Los Angeles, Calif. Meets on second Wednesday of each month at County Society Building.

**RADIOLOGICAL SECTION, SOUTHERN MEDICAL ASSOCIATION**
*Secretary*, Dr. Roy G. Giles, Temple, Texas.

**BROOKLYN ROENTGEN RAY SOCIETY**
*Secretary*, Dr. E. Mendelson, 120 E. 19th St., Brooklyn, N. Y. Meets monthly on first Tuesday, October to April.

**BUFFALO RADIOLOGICAL SOCIETY**
*Secretary-Treasurer*, Dr. Joseph S. Gian-Franceschi, 610 Niagara St., Buffalo, N. Y. Meets second Monday of each month except during summer months, place of meeting selected by the host.

**CHICAGO ROENTGEN SOCIETY**
*Secretary*, Dr. R. G. Willy, 1138 N. Leavitt. Meets second Thursday of each month October to May inclusive at the Palmer House.

**CINCINNATI RADIOLOGICAL SOCIETY**
*Secretary*, Dr. J. E. McCarthy, 707 Race St., Cincinnati, Ohio. Meets third Tuesday of each month, October to May, inclusive.

**CLEVELAND RADIOLOGICAL SOCIETY**
*Secretary*, Dr. H. A. Mahrer, 10515 Carnegie Ave. Meets at 6:30 P.M. at Mid-Day Club rooms on fourth Monday each month, October to April, inclusive.

**DENVER RADIOLOGICAL CLUB**
*Secretary*, Dr. E. A. Schmidt, 4200 E. 9th Ave., Denver, Colo. Meets third Tuesday of each month.

**DETROIT ROENTGEN RAY AND RADIUM SOCIETY**
*Secretary*, Dr. E. R. Witwer, Harper Hospital. Meets monthly on first Thursday from October to May, at Wayne County Medical Society Building.

**FLORIDA STATE RADIOLOGICAL SOCIETY**
*Secretary*, Dr. J. H. Lucinian, 403 Huntington Bldg., Miami. Meetings in May and November.

**GEORGIA RADIOLOGICAL SOCIETY**
*Secretary*, Dr. R. C. Pendergrass, Prather Clinic Bldg., Americus, Ga. Meets in November and at annual meeting of Medical Association of Georgia in the spring.

**ILLINOIS RADIOLOGICAL SOCIETY**
*Secretary*, Dr. E. P. Halley, Decatur and Macon County Hospital, Decatur, Ill. Meetings held quarterly, time and place designated by president.

**INDIANA ROENTGEN SOCIETY**
*Secretary*, Dr. C. C. Taylor, 23 E. Ohio St., Indianapolis, Ind. Meeting held the second Sunday in May annually.

**LONG ISLAND RADIOLOGICAL SOCIETY**
*Secretary*, Dr. Marcus Wiener, 1430-48th St., Brooklyn, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:30 P.M.

**MICHIGAN ASSOCIATION OF ROENTGENOLOGISTS**
*Secretary*, Dr. C. S. Davenport, St. Lawrence Hospital, Lansing. Three meetings a year, Fall, Winter, Spring.

**MILWAUKEE ROENTGEN RAY SOCIETY**
*Secretary*, Dr. I. I. Cowan, Mt. Sinai Hospital, Milwaukee, Wis. Meets monthly on first Friday at University Club.

**MINNESOTA RADIOLOGICAL SOCIETY**
*Secretary*, Dr. H. M. Weber, Mayo Clinic, Rochester, Minn.

**NEBRASKA RADIOLOGICAL SOCIETY**
*Secretary*, Dr. D. A. Dowell, Medical Arts Bldg., Omaha, Nebr. Meets first Wednesday of each month, at 6 P.M., at either Omaha or Lincoln.

**NEW ENGLAND ROENTGEN RAY SOCIETY**
*Secretary*, Dr. A. O. Hampton, Massachusetts General Hospital, Boston, Mass. Meets monthly on third Friday, Boston Medical Library.

**RADIOLOGICAL SOCIETY OF NEW JERSEY**
*Secretary*, Dr. W. J. Marquis, 198 Clinton Ave, Newark. Meets annually at time and place of State Medical Society. Mid-year meetings at place designated by president.

**NEW YORK ROENTGEN SOCIETY**
*Secretary*, Dr. R. D. Duckworth, 170 Maple Ave., White Plains, N. Y. Meets monthly on third Monday, New York Academy of Medicine, at 8:00 P.M.

**NORTH CAROLINA ROENTGEN RAY SOCIETY**
*Secretary*, Dr. Major Fleming, Rocky Mount, N. C. Annual meeting at time and place of State Medical Society. Mid-year scientific meeting at place designated.

**CENTRAL NEW YORK ROENTGEN RAY SOCIETY**
*Secretary*, Dr. C. F. Potter, 820 S. Crouse Ave., Syracuse. Three meetings a year—January, May, November.

**PACIFIC ROENTGEN CLUB**
*Secretary*, Dr. L. H. Garland, 450 Sutter St., San Francisco, Calif. Meets annually, during meeting of California Medical Association.

**PENNSYLVANIA RADIOLOGICAL SOCIETY**
*Secretary*, Dr. L. E. Wurster, 416 Pine St., Williamsport, Pa. Annual meeting, June 2 and 3, 1939. Bedford Springs Hotel, Bedford, Pa.

**PHILADELPHIA ROENTGEN RAY SOCIETY**
*Secretary*, Dr. B. R. Young, Temple University Hospital. Meeting first Thursday of each month from October to May inclusive, at 8:15 P.M., in Thompson Hall, College of Physicians, 19 S. 22d St

**PITTSBURGH ROENTGEN SOCIETY**
*Secretary*, Dr. H. W. Jacox, 4800 Friendship Ave., Meetings held second Wednesday each month, 4:30 P.M., October to June at various hospitals.

**ROCHESTER ROENTGEN RAY SOCIETY, ROCHESTER, N. Y.**
*Secretary*, Dr. S. C. Davidson, 277 Alexander St., Meets on second Thursday from October to May, inclusive, 8 P.M., Rochester Academy of Medicine Building.

**ST. LOUIS SOCIETY OF RADIOLOGISTS**
*Secretary*, Dr. W. K. Mueller, University Club Bldg. Meets fourth Wednesday of October, January, March and May, at a place designated by the president.

**SAN FRANCISCO RADIOLOGICAL SOCIETY**
*Secretary*, Dr. L. H. Garland, 450 Sutter St., San Francisco. Meets monthly on first Monday at 7:45 P.M., alternately at Toland Hall and Lane Hall.

* Secretaries of Societies not here listed are requested to send the necessary information to the Editor.

South Carolina X-Ray Society
*Secretary*, Dr. Hillyer Rudisill, Jr., Roper Hospital, Charleston. Meets in Charleston on first Thursday in November, also at the time and place of South Carolina State Medical Association.

Tennessee Radiological Society
*Secretary*, Dr. F. B. Bogart, 311 Medical Arts Bldg. Chattanooga, Tenn. Meets annually at the time and place of the Tennessee State Medical Association.

Texas Radiological Society
*Secretary*, Dr. H. C. Harrell, 517 Pine St., Texarkana, Texas. Next regular meeting in Temple, Texas, 1939.

University of Michigan Department of Roentgenology Staff Meeting
Meets each Monday evening from September to June, at 7 P.M. at University Hospital.

University of Wisconsin Radiological Conference
*Secretary*, Dr. E. A. Pohle, 1300 University Ave., Madison, Wis. Meets every Thursday from 4:00–5:00 P.M., Room 301, Service Memorial Institute.

Virginia Radiological Society
*Secretary*, Dr. V. W. Archer, University Hospital, University, Va. Meets annually in October.

### Cuba

Sociedad Cubana de Radiologia y Fisioterapia
*Secretary*, Dr. Francisco Padron, Enrique, Villuendas 64, Havana, Cuba. Meets monthly in Havana.

### British Empire

British Institute of Radiology Incorporated with the Röntgen Society
Meets monthly on third Thursday, from November to June inclusive, at 8:15 P.M., 32 Welbeck St., London.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets on the third Friday of each month during the winter at 8:15 P.M. at the Royal Society of Medicine, 1, Wimpole St., London, W. 1.

Faculty of Radiologists
*Secretary*, Dr. Barbara M. Key, 32 Welbeck St., London, W.1, England.

Section of Radiology and Medical Electricity, Australasian Medical Congress
*Secretary*, Dr. H. M. Cutler, 139 Macquarie St., Sydney, New South Wales.

Radiological Section of the Victorian Branch of the British Medical Association
*Secretary*, Dr. Keith Hallam, St. George's Hospital, K.E.W., Melbourne, E. 4, Victoria, Australia. Meets monthly from March to Nov. incl. for scientific discussion.

Canadian Association of Radiologists
*Secretary*, Dr. A. C. Singleton, Medical Arts Bldg., Toronto, 5, Ontario.

Section of Radiology, Canadian Medical Association
*Secretary*, Dr. C. M. Jones, Inglis St., Ext., Halifax, N.S.

Radiological Section, New Zealand British Medical Association
*Secretary*, Dr. Colin Anderson, Invercargill, New Zealand. Meets annually.

### Continental Europe

Belgian Society of Roentgenology
*Secretary*, Dr. J. Boine, Avenue des Alliés, 134, Louvain (Belgium).
Meets monthly on second Sunday at d'Egmonds Palace, Brussels, except in the summertime.

Sociedad Espanola de Radiologia y Electrologia
*Secretary*, Dr. J. Martin-Crespo, Fuencarral, 7, Madrid, Spain. Meets monthly in Madrid.

Société de Radiologie Médicale de France
Meets monthly on second Tuesday, except during months of August and September, 12 Rue de Seine, Paris.

Société Suisse de Radiologie (Schweizerische Röntgen-Gesellschaft)
*Secretary* for French language, Dr. A. Grosjean, La Chaux de Fonds.
*Secretary* for German language, Dr. Scheurer, Molzgasse, Biel. Meets annually in different cities.

Société Francaise d'Electrothérapie et de Radiologie Médicale
Meets monthly on fourth Tuesday, except during month of August and September, 12 Rue de Seine, Paris.

Association of German Roentgenologists and Radiologists in Czecho-Slovakia
*Secretary*, Dr. Walter Altschul, German University, Prague, 11.52.

Deutsche Röntgen-Gesellschaft (Gesellschaft für Röntgenkunde und Strahlenforschung)
Meets annually in April, alternating one year in Berlin, one year in some other German city. Meets in addition every two years with the Gesellschaft deutscher Naturforscher und Aerzte.
*Permanent Secretary*, Professor Dr. Haenisch, Klopstockstrasse 10, Hamburg, Germany.

Süd- und Westdeutsche Röntgensellschaft
Meets annually in different cities.

Nord- und Ostdeutsche Röntgengesellschaft
Meets annually in different cities.

Dutch Society of Electrology and Roentgenology
Holds two meetings a year in Amsterdam, one in the Spring, and one in the fall.

Societa Italiana Radiologia Medica
*Secretary*, M. Ponzio, University of Turin, Prof. Turin

Societatea Romana de Radiologie si Electrologie
*Secretary*, Dr. Oscar Meller, Str. Banul Mărăcine, 30, S. I., Bucuresti, Roumania.
Meets second Monday in every month with the exception of July and August.

All-Russian Roentgen Ray Association, Leningrad, USSR in the State Institute of Roentgenology and Radiology, 6 Roentgen St.
*Secretaries*, Drs. S. A. Reinberg and S. G. Simonson. Meets annually.

Leningrad Roentgen Ray Society
*Secretaries*, Drs. S. G. Simonson and G. A. Gusterin. Meets monthly, first Monday at 8 o'clock State Institute of Roentgenology and Radiology, Leningrad.

Moscow Roentgen Ray Society
*Secretaries*, Drs. L. L. Holst, A. W. Ssamygin and S. T. Konobejevsky. Meets monthly on first Monday at 8 o'clock.

Polish Society of Radiology
*Secretary*, Dr. Jan Kochanowski, 45 Gornoslazka St., Warsaw. Meets annually.

Warsaw Section, Polish Society of Radiology
*Secretary*, Dr. B. Krynski, 11 Zielna St.
Meets once a month except in the summertime.

Scandinavian Roentgen Societies
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association. Each of the following societies, with exception of the Denmark Society, meets every second month except in the summertime:

Society of Medical Radiology in Sweden
Meets in Stockholm.

Society of Medical Radiology in Norway
Meets in Oslo.

Society of Medical Radiology in Denmark
*Secretary*, Dr. G. Biering, Copenhagen.
Meets the second Wednesday of each month from October to July in Copenhagen, at 8 o'clock in the State Institute of Roentgenology.

Society of Medical Radiology in Finland
Meets in Helsingfors.

Vienna Roentgen Society
Meets first Wednesday of each month, at 6:30 P.M. at Zentral-Röntgen Institut des allgemeinen Krankenhauses Alserstrasse 4.

### Orient

Japan X-Ray Association
c/o Orthopedic Surgery, Tokyo Imperial University. Meets annually in April.

Kinki Roentgen-Abend Society
Director, Dr. Prof. Taiga Saito, Ogawaoike Tyoto Japan. Meets bi-monthly on third Sunday.

## BULLETIN OF THE INTER-SOCIETY COMMITTEE FOR RADIOLOGY

### WHO SHALL PRACTICE MEDICINE?

Not the least important problem confronting the profession of radiology today is the question of the status and domain of the lay technician in radiological practice. It is a question which arises again and again, in one phase or another, as the Inter-Society Committee approaches professional and socio-economic situations in various sections of the country. It is a question which urgently demands solution.

A recent article by Dr. Albert A. Rayle, a portion of which is reprinted herewith by permission of the *Journal of the Medical Association of Georgia*, states the problem in clear fashion. In connection with Dr. Rayle's straight-forward comments, it is interesting to compare an article in a similar vein written more than ten years ago by the present chairman of the Inter-Society Committee for Radiology, Dr. Arthur C. Christie.

Lest some misunderstanding occur, it may be well to define the term "lay technician" before quoting from the two papers mentioned above. Certainly neither the Inter-Society Committee nor any individual radiologist has anything less than the highest esteem and appreciation for the invaluable services of the technician whom he employs and upon whose conscientious loyalty and skill he depends for assistance in the practice of his profession. The function of these individuals fills an indispensable ancillary rôle in the practice of radiology.

But, when the lay technician attempts the practice of radiology upon his own part, without the supervision of a licensed physician radiologist, he or she becomes a quack, proposing to render a service for which the individual is unqualified, untrained, and incompetent. He becomes a "limited practitioner" and, like other cultists, he professes to possess special ability in a particular field without having gone to the trouble and expense of equipping himself with the essential medical background.

The question of the non-medical practitioner of radiology is one which threatens the very survival of a recognized and important specialty in medicine. The evil has been fostered by numerous modern developments in the practice of medicine, such as the industrial clinic where a lay technician examines and reports on cases treated under workmen's compensation laws, and the attempts to divide the specialty into technical and professional phases under group hospitalization plans. If these situations are to be corrected, and if further unsound tendencies are to be forestalled, radiological practitioners themselves must point the way. If radiology is, as we contend, a clinical specialty demanding medical training instead of a technical laboratory procedure to be performed by laymen, then radiologists must demonstrate to their medical colleagues that such is the case.

It is somewhat paradoxical that the article published by Dr. Christie when he was editor of the AMERICAN JOURNAL OF ROENTGENOLOGY AND RADIUM THERAPY in 1927 contains some answers to the questions posed by Dr. Rayle in his article written twelve years later. If this be irony, it simply goes to show that there remains much room for progress in solution of a vexing problem.

From Dr. Rayle's paper, presented before a meeting of the Fulton County Medical Society, Atlanta, we quote as follows:

> There is an old feeling, still ingrained in the make-up of a physician, that he should devote his thoughts to the scientific phases of his work and let the economic phases take care of themselves. Perhaps this is the reason physicians are reputedly poor business men. But now the economic phases have thrust themselves on us and we have to talk about them, however distasteful it may be.
>
> We physicians have nothing to sell but our services. We have spent many years and many thousands of dollars to make those services worth something to the public—and we are

entitled to sell them in fair market, without improper restrictions or unfair competition.

Therefore we are all interested in what we call socialized medicine, which, for our purposes, we will define as any system whereby either the professional or economic aspects of practice are controlled by laymen. The two go hand in hand, for economic control will lead to professional control. It is axiomatic that the man who pays the fiddler eventually will call the tune.

For most of you, socialized medicine is something to talk about at medical meetings. For us in radiology it has arrived in one form or another. What I shall say will be primarily about radiology, but it applies also to other fields, and it is only a matter of time until it will concern every one of you.

Realizing the dangers surrounding radiology from an economic standpoint, the four national societies have organized the Inter-Society Committee for Radiology, whose sole purpose is to deal with matters affecting the economics of radiologic practice. This committee has asked and obtained the support of the Georgia Radiological Society, which at its last meeting appointed a committee to deal with the subject for which I speak tonight.

The Georgia committee decided to limit its field to four topics. Of these, our first two problems are in process of adjustment and need not concern us in this discussion.

Cur third problem, the lay-radiologist may be stated as a formula. 1. Radiology is the practice of medicine; 2. Medicine legally may be practiced only by those physicians holding a license. 3. But laymen practice radiology. It does not come out even, or make sense. Why? Because certain members of the medical profession support and defend the lay-radiologist. Why? Because the lay-radiologist can and does offer inducements which medical men can not ethically offer. You may ask why we do not hail the lay-radiologist to court. The reason is that if we do, he can and will employ a cheap doctor to go in partnership with him and sign his reports. As long as there are doctors who will do this, we can accomplish nothing.

Suppose we set up a hypothetical situation equally as logical. I believe any one of you will agree that any bright young man with a reasonable amount of training could learn to take out tonsils, appendices, gall-bladders and uteri in an acceptable manner from a standpoint of surgical technic. Well then, why not train up a lot of laymen as surgical technicians? Obviously, you would say—"Such a man would have no medical background. He might know how to take out an appendix but he would not know when." Now that is just exactly the objection we offer to the lay-radiologist. He may be an excellent technician, he may have picked up a working knowledge of x-ray diagnosis, but he certainly cannot have acquired a medical background.

But suppose we carry our surgical technician idea a bit farther. Say we have these trained surgical technicians. The internist might say—"Well this is great. I can make a diagnosis. I know when to operate. These fellows know how to operate. We will work together. I will send my patient to the surgical technician. He will operate for a few dollars a case. Why should I let the surgeon milk the cream from my patients?" Why, my friends, if any such system as this were seriously proposed, surgeons would be wringing their hands from Maine to California. And yet some surgeons support the same set-up in radiology.

From Dr. Christie's editorial[1], we quote the following:

It is well known that there is a widespread and probably growing tendency to depend upon lay technicians, not only for the technical work which is their proper field, but for opinions on the roentgen findings, and even for diagnosis of the underlying pathological process. The medical profession itself is largely to blame for the development of this abuse just as it has been responsible by neglect of certain fields for the success of most of the medical cults. Roentgenologists themselves must bear at least a part of the blame for the assumption of medical functions by the technician. It is true that many roentgenologists take a very serious view of their responsibilities as medical consultants and follow the general practice of seeing every patient referred to them for roentgen-ray diagnosis, and their final opinion is based not only upon the roentgen-ray findings but upon a knowledge of the history of the case and all other information available. But on the other hand, there are many who base their entire report upon the roentgen findings alone, perhaps even upon films alone, never having seen the

[1] Christie, A. C. Who shall practice medicine? AM. J. ROENTGENOL. & RAD. THERAPY, 1927, *18*, 464.

patient and having no knowledge whatever of the previous history, the course of the disease, nor the patient's present condition. There are, of course, situations in which the above course is not censurable, where the final results are to be evaluated by a well-trained internist who is capable of giving all information its due weight. Even in such instances, however, it is probable that better results are achieved by close cooperation and consultation between the internist and the roentgenologist than can be obtained by the roentgenologist's submitting a report based upon roentgenologic examination alone. It is a fact that in many offices and hospitals the only person who really sees the patient who is referred for roentgen examination is the roentgen technician, and in many such places the technician's opinion is the only one sought. It is therefore not to be wondered at that the general physician who refers patients to roentgenologists for examination gradually comes to depend upon the technician for his findings rather than upon the doctor and that he finally adopts the practice of sending his patients to a commercial roentgen-ray laboratory or depends upon the report of a lay technician in a hospital. Only a little reflection, however, will show that such practice is not in line with general medical progress and that it carries actual and potential dangers of great importance. At the present time all over this country the roentgen ray is being used for diagnosis and treatment of disease not only by variously trained lay technicians but by the practitioners of almost all of the medical cults whether or not they are licensed to practice medicine. In recent times it is reported that even "beauty parlors" have used the roentgen ray extensively for the removal of superfluous hair.

The cure for the "technician evil" lies entirely within the medical profession. It will undoubtedly persist so long as there are a considerable number of physicians who do not realize that there is a wide gap between the films produced by the technician and their translation into terms of underlying pathology. The cure of the evil will be in sight when physicians realize that they are fostering another class of irregular, ignorant, unlicensed medical practitioners who are already rendering reports of roentgen-ray findings directly to patients and in some instances even using the roentgen ray as a therapeutic agent. In the meantime, the roentgenologist who takes a high view of his obligations would do well to review his own attitude and practice in the employment of technicians.

MAC F. CAHAL
*Executive Secretary*
Inter-Society Committee for Radiology

# BOOK REVIEWS

*Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers as space permits.*

THE RADIOLOGY OF PULMONARY TUBERCULOSIS. By J. E. Bannen, M.B., Ch.B., D.M.R.E., Hon. Radiologist, Hull Royal Infirmary; Radiologist, Hull Corporation Hospitals and Tuberculosis Clinics, East Riding County Council and Raywell Sanatorium, Hull Corporation Mental Hospital, Willerby, Hull and Sculcoates Dispensary. Cloth. Price, $4.50. Pp. 156, with 39 illustrations. Baltimore: William Wood and Company, 1937.

If the experienced roentgenologist expects to glean new facts or advanced ideas from this book he will be disappointed. But if he is looking for a compact book which thoroughly covers the essentials of the subject he will be rewarded. Bannen's work is of the class usually designated as elementary and is admirably suited for use as a text by medical students, interns or others wishing a thorough groundwork in the essentials of chest diagnosis. For while this work deals primarily with tuberculosis it also considers complications such as atelectasis and effusions and allied lesions such as pneumoconiosis. Therefore one who studies this text carefully has good preparation for general chest diagnosis.

In an effort at completeness some seemingly superfluous matters are introduced such as physical examinations, findings on auscultatory percussion and the like, which every student may be assumed to have learned in his medical course. Technique of the sedimentation test is of value as general information but not of much practical use to a roentgenologist.

The illustrations are plentiful and the detail is as good as could be expected for their size, there being two to a page, but the author has sensibly made them all negative reductions corresponding to the practical usage of examining negatives.

No really unfavorable criticism of the book can be made and it is recommended as a very complete elementary text on the roentgenology of tuberculosis, with some associated ideas included for general teaching.

E. W. HALL

TUBERCULOSIS AMONG CHILDREN AND YOUNG ADULTS. By J. Arthur Myers, Ph.D., M.D., F.A.C.P., Chief of Medical Staff and Director of Tuberculosis Activities, Lymanhurst Health Center; Professor of Preventive Medicine, University of Minnesota. Second Edition. Cloth. Price, $4.50. Pp. 401, with 71 illustrations. Springfield, Illinois: Charles C. Thomas, 1938.

The second edition of this book has been materially enlarged to cover the recent developments in the diagnosis, treatment and prevention of tuberculosis in children and young adults, along with a very comprehensive bibliography.

The book is divided into three parts. Part one deals with tuberculosis in infancy, part two with tuberculosis in childhood, and part three with tuberculosis among young adults, and other considerations. Each part is divided into chapters dealing with the various types of infection, their mode of entry, diagnosis, treatment and prevention.

The author has used as collaborators C. A. Stewart, Clinical Professor of Pediatrics, and Paul W. Giessler, Assistant Professor of Orthopedic Surgery of the University of Minnesota.

This book embraces its field as thoroughly as could be expected of any small one volume book. Its brevity necessarily means that much technical detail has been omitted. This makes it more appealing to physicians not in tuberculosis work and to students, although, by its large bibliography, the specialist in this field will find it very useful.

There is one exception to be taken. On page 19, the author speaks of the "X-ray camera." This certainly is not a very scientific expression and should be corrected in future editions.

EDGAR M. MCPEAK

THE PITUITARY GLAND: AN INVESTIGATION OF THE MOST RECENT ADVANCES. (Association for research in Nervous and Mental Disease. Vol. XVII of a Series of Research Publications.) The Proceedings of the Association, New York, December 28th and 29th, 1936.

Editorial Board: Walter Timme, Angus M. Frantz, Clarence C. Hare. Cloth. Price, $10.00. Pp. 764, with 160 illustrations. Baltimore: The Williams & Wilkins Co., 1938.

This book on the pituitary gland is a very comprehensive work and the contents are divided into three sections. Section one takes up the anatomy with a very fine chapter on the glands of the brain, with especial reference to the pituitary gland by Dr. Frederick Tilney. The finer anatomy and histology are taken up in this section.

The second section concerns the physiology of the gland and excellent contributions are made by leaders in endocrine research such as Herbert M. Evans, Selye, Hisaw, Collip, Engle, Kurzrok, P. E. Smith, and many others. There is an interesting chapter by Bissonnette on the influence of light upon pituitary activity.

The third section concerns general considerations of the gland such as pituitary disturbances in relation to personality, behavior changes produced in the rat by hypophysectomy, the pituitary basophilism of Cushing, and pituitary cachexia. The roentgen therapy of pituitary tumors is taken up by Dyke and Hare.

This is a very fine review, is well illustrated, and serves to bring the subject up to date. The book is a worth while addition to every physician's library, no matter what his field of medicine.

Robert C. Moehlig

L'exploration radiologique des tumeurs de l'hypopharynx et du larynx. By Pierre Charles Huet and Maurice Peri. Report to the French Society of Oto-Rhino-Laryngology, Congress of 1938. Vol. 52, Part 1. Paper. Pp. 244, with illustrations. Paris: Boutin, 1938.

Any radiologist or laryngologist who is interested, as both should be, in the roentgen demonstration and diagnosis of hypopharyngeal and laryngeal tumors will find in this book a complete, well organized and authoritative exposition of the method and its capabilities. Certainly the procedure is not novel, for, as the authors point out, its employment began within a year after the roentgen rays were discovered, but only in recent years have its practical potentialities become apparent. Even today these potentialities are seldom realized, for the method is not often applied and then only somewhat perfunctorily, and without expectation that it will yield highly significant information. But the radiologist who reads this book can scarcely fail to be inspired with the belief that more assiduous cultivation of this field will be well worth while.

Rather striking is the variety of applicable techniques, including roentgenoscopy or roentgenography without aids, also during insufflation, during deglutition of barium pastes and after injection of lipiodol, as well as roentgenography with contact films in the pharynx.

To obtain satisfactory results any of these techniques must be executed with judgment and care, and the authors describe them with painstaking detail. The roentgen appearance of the normal pharynx and larynx with each technique is adequately presented, and thereafter the roentgenologic manifestations of benign and malignant tumors, variously situated, are fully described. A profusion of excellent roentgenograms and drawings, with fully descriptive legends and abstracts of case histories, adds greatly to the instructive value of the book.

B. R. Kirklin

Affections non ulcéreuses du duodénum. By I. Pavel, Faculty of Medicine, Bucharest, and A. Paunesco-Podeano, Formerly Intern of the Bucharest Hospitals and Physician to the Brancovan Hospitals. Preface by J. Ch. Roux. Paper. Price, 50 fr. Pp. 204, with 57 illustrations. Paris: Masson et Cie, 1938.

Quite fittingly this treatise has a preface by Dr. J. Ch. Roux, who in conjunction with Professor Duval and Dr. Béclére published a well known volume on similar lines several years ago. Roux deplores the general tendency to limit the study of duodenal pathology to duodenal ulcer. He admits that ulcer is a common lesion, for it is found in from 5 to 10 per cent of all autopsies, but he points out that many less common affections are also important. He holds that the transit of food through the duodenum should be particularly rapid and that any delay, whether due to external compression, a kink, a congenital malformation, a persistent spasm or a paralytic dilatation, leads to very characteristic troubles.

Pavel and Paunesco-Podeano begin their book with a chapter on the physiology of the duodenum and discuss its external secretion, endocrine rôle, absorptive function, bacte-

riology and motility. They then deal systematically with the various forms of duodenitis, including pseudo-ulcerous, hemorrhagic, chronic with icterus, catarrhal icteric, duodenitis related to hepatic cirrhosis, phlegmonous duodenitis and the infectious varieties due to charbon, tuberculosis, etc. Then follow chapters or sections on diverticulosis, mechanical stasis, periduodenitis, functional stasis, hypotonic stasis, cancer, sarcoma, benign tumors, lymphogranulomatosis, congenital anomalies and parasites. Each of these affections is thoroughly considered from the pathologic, clinical and roentgenologic viewpoints.

To the reviewer, who has been keenly interested in duodenitis and has tried to contribute to an understanding of its roentgenologic manifestations, the chapters dealing with this theme were particularly impressive. The authors' classification of the disease into several varieties seems to be well founded, and its roentgenologic aspects as noted by various observers are described clearly and comprehensively. The other sections of the book also merit commendation, for the respective analyses are complete and practical, and the illustrations are well selected and instructive.

B. R. Kirklin

## BOOKS RECEIVED

A Textbook of Neuro-radiology. By Cecil P. G. Wakeley, D.Sc., F.R.C.S., F.A.C.S., F.R.A.C.S. (Hon.), Fellow of King's College, London, Senior Surgeon, King's College Hospital and West End Hospital for Nervous Diseases, etc., and Alexander Orley, M.D., D.M.R.E., Fellow of the British Association of Radiologists; Radiologist, West End Hospital for Nervous Diseases, etc. Cloth. Price, $8.00. Pp. 336, with 229 illustrations. Baltimore: William Wood and Company, 1938.

Chronic Diseases of the Abdomen: A Diagnostic System. By C. Jennings Marshall, M.S., M.D. (Lond.), F.R.C.S. (Eng.), Surgeon, Charing Cross Hospital and Victoria Hospital for Children; Surgical Consultant, L.C.C., and Bromley District Hospital; Examiner in Surgery, London University and Victoria University, Manchester. Cloth. Price, $6.00. Pp. 247, with 131 illustrations. Boston: Little, Brown & Company, 1939.

Roentgen Diagnosis of the Extremities and Spine. (Ann. Roentgenol., Vol. xvii.) By Albert B. Ferguson, M.D., Director of Roentgenology, New York Orthopaedic Hospital; Instructor in Orthopaedic Surgery, College of Physicians and Surgeons, Columbia University. Cloth. Price, $12.00. Pp. 435, with 513 illustrations. New York: Paul B. Hoeber, Inc., 1939.

A Manual of Roentgen Diagnosis. By Kenneth S. Davis, M.D., Los Angeles. Cloth. Pp. 160, with 279 illustrations. Los Angeles: Kenneth S. Davis, 1938.

Le duodénum: Atlas de radiologie clinique. Par P. Cottenot, Médecin radiologiste de l'Hopital Broussais, Max Lévy, Ancien chef de laboratoire à la Faculté de Médecine, et Ed. Chérigié, Assistant de Radiologie de l'Hopital Broussais. Préface de M. Robineau. Cloth. Price, 285 fr. Pp. 224, with 496 illustrations. Paris: G. Doin & Cie, 1938.

Digrafía: Nuevo método radiográfico para el estudio de los órganos móviles. By Guido Pollitzer. Paper. Pp. 104, with 41 illustrations. Buenos Aires: Imprenta Amorrortu, 1937.

End-results in the Treatment of Gastric Cancer: An Analytical Study and Statistical Survey of Sixty Years of Surgical Treatment. By Edward M. Livingston, B.Sc., M.D., Associate Visiting Surgeon, Bellevue Hospital, New York; Assistant Clinical Professor of Surgery, New York University College of Medicine, and George T. Pack, B.Sc., M.D., F.A.C.S., Attending Surgeon, Memorial Hospital, New York City; Assistant Professor of Clinical Surgery, The School of Medicine, Yale University, New Haven and Cornell University Medical College, New York City. With a Foreword by Bowman C. Crowell, M.D., Associate Director, American College of Surgeons. Cloth. Price, $3.00. Pp. 179, with numerous charts. New York: Paul B. Hoeber, Inc., 1939.

Die Röntgentiefentherapie. Unter Mitarbeit von Fachgenossen zusammengestellt von Professor Hans Holfelder, O.Ö. Professor für allgemeine klinische Röntgenkunde an der Johann-Wolfgang-Goethe-Universität, Frankfurt a. M. Paper, price R.M. 27; bound, price R.M. 29. Pp. 341, with 264 illustrations. Leipzig: Georg Thieme, 1938.

Pyrétothérapie. Par Charles Richet, Professeur agrégé à la Faculté de Médicine de Paris, Médecin des Hôpitaux de Paris, Jean Surmont, Médecin Electro-radiologiste des Hôpitaux de Paris, et Pierre Le Gô, Electro-radiologiste des Asiles de la Seine. Paper. Price, 50 fr. Pp. 192, with illustrations. Paris: Masson et Cie, 1938.

La impregnacion visceral mediante sales radioactivas: Método de exploración radiológica. By Eduardo L. Lanari, Miguel Eduardo Jörg and Juan Alberto Aguirre. Paper. Pp. 349, with 129 illustrations. Buenos Aires: Actualidad Médica Mundial, 1937.

A Historical Chronology of Tuberculosis. By Richard M. Burke, M.D., State Veterans Hospital, Sulphur, Oklahoma. Cloth. Price, $1.50. Pp. 84. Springfield, Illinois: Charles C. Thomas, 1938.

Anatomy of the Human Lymphatic System. By H. Rouvière, Professor of Anatomy at the Medical Faculty of Paris, France. A Compendium. Tranlsated from the original *Anatomie des lymphatiques de l'homme* and rearranged for the use of students and practitioners. By M. J. Tobias, Formerly of the Department of Anatomy, New York Univeristy, School of Medicine, Assistant Radiologist, Montefiore Hospital, New York. Cloth. Price, $4.00. Pp. 318, with 129 illustrations. Ann Arbor, Michigan: Edwards Brothers, Inc., 1938.

Textbook of Anatomy and Physiology. By Diana Clifford Kimber, Carolyn E. Gray, A.M., R.N., and Caroline E. Stackpole, A.M., Associate in Biology, Teachers College, Columbia University. Tenth edition, revised and rewritten. Cloth. Price, $3.00. Pp. 643, with 276 illustrations. New York: The Macmillan Company, 1938.

The Physiology of Exercise: A Text-Book for Students of Physical Education. By James Huff McCurdy, A.M., M.D., M.P.E., Director of Physical Education, Springfield College, Springfield, Mass., etc., and Leonard A. Larson, B.A., B.P.E., M.Ed., Ph.D., Professor of Health and Physical Education, Springfield, College, Springfield, Mass. Third edition, thoroughly revised. Cloth. Price, $3.75. Pp. 349. Philadelphia: Lea & Febiger, 1939.

A Textbook of Nursing Practice. By Hester K. Frederick, R.N., Assistant Superintendent of Nurses, The Johns Hopkins Hospital School of Nursing, and Ethel Northam, R.N., Director of the Nursing Arts, The Johns Hopkins Hospital School of Nursing. Second edition, revised. Cloth. Price, $3.00. Pp. 418, with 56 illustrations. New York: The Macmillan Company, 1938.

The Vitamins and Their Clinical Applications. By Prof. Dr. W. Stepp, Director of the I. Medical Clinic, University of Munich; Doz. Dr. Kühnau, Director of the Municipal Institute for Balneology and Metabolism, Wiesbaden, and Dr. H. Schroeder, Associate at the I. Medical Clinic, University of Munich. Translated by Herman A. H. Bouman, M.D., Minneapolis, Minnesota. Cloth. Pp. 173. Milwaukee, Wisconsin: The Vitamin Products Co., 1938.

Bericht über die konstituierende Sitzung der Internationalen Akademie für das artzliche Fortbildungswesen. Budapest, April 23–28, 1938. Redigiert von Dr. K. Blome, Präsident and Prof. Dr. C. Adam, Generalsekretär, des permanenten Büros. Cloth. Pp. 328, with 27 illustrations. Jena: Gustav Fischer, 1938.

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# DEPARTMENT OF TECHNIQUE

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## SUGGESTED MODIFICATIONS OF TECHNIQUE FOR ROENTGEN PHOTOGRAPHY

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*Macon County Tuberculosis Sanatorium*
DECATUR, ILLINOIS

THE fact that the earliest forms of tuberculous infiltration of the lung parenchyma are usually asymptomatic has brought about case-finding activities that center upon the chest roentgenogram.[1]

For the reason, too, that in large group surveys, costs are apt to be high, the tuberculin test is used to eliminate non-reactors with savings in roentgen film costs which are proportionate to the infection rate of the age groups tested.

Beginning with the early 'teen age, the percentage of tuberculin reactors is sufficiently high so that for some communities it becomes necessary to adopt cheaper roentgenographic methods with which to provide the supplementary examination. So-called "paper films" have been developed for use when, for economic reasons, stereoroentgenograms or single celluloid films are unavailable. Various investigating committees[2] have found these to be technically inferior to celluloid films and that perhaps some of the smaller and more obscure lesions might not be recognized. Actually, paper film costs are approximately 50 per cent of that for the celluloid type, and, in the average roentgen laboratory the paper films prove cumbersome in the darkroom as well. Even roentgenoscopy, with its low milliamperage (5–10 ma.) contrast values, and distortion effects from lessened focal spot-screen distances, is occasionally used when other roentgen methods have been economically impossible.

De Abreu, Rio de Janeiro, has recently made practical application of the original suggestions of Cole, Leven, Reynolds, Commodon, and others, for photographing the roentgenoscopic image.[3] The apparatus is simple, relatively inexpensive, and units

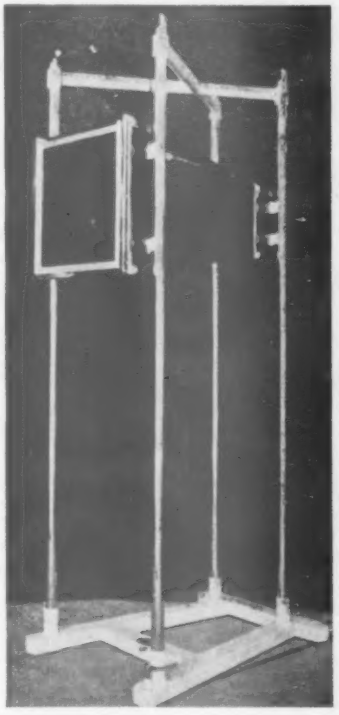

Fig. 1. Except for supporting stand the de Abreu unit is portable and small.

have been in daily operation in three cities of Brazil, with five more in contemplation (see Fig. 1). They have also been used in connection with dispensary units in Montevideo, Buenos Aires, Havana, Berlin and Frankfurt.[4] The method provides for 1,000 exposures of 35 mm. size on a single reel

with utilization of ordinary roentgen-ray equipment with the addition of a portable unit which houses the camera (Contax, Leica, or Exacta 1:1.2; 1:1.5) and a fluoroscopic screen set at proper focal distance, guarded from sources of light.

We have sought to prove the practicability of the unit by constructing temporary apparatus in accordance with the designs and specifications of the originator and the addition of a camera to existing roentgen-ray equipment and were able to successfully duplicate de Abreu's techniques which utilized the following technical factors: camera-screen distance, 90 cm.; focal spot-screen distance, 60 cm.; milliamperage, 50; kilovoltage (peak) (variable); exposure time, 0.15 sec.; film, Isochrom. Such techniques, however, have definite over-penetration values (see Fig. 2) and therefore do not satisfy basic requirements for the fairly satisfactory chest film which should preserve without undue distortion bronchovascular markings which, with adequate contrast, must be visualized from hilum to lateral chest border, and from apex to diaphragmatic crest.[5]

FIG. 2

FIG. 3

FIGS. 2 and 3. De Abreu technique films show over-penetration (Fig. 2) and suggest the practicability of the addition of one or more favorable factors as in longer tube-screen distance, higher milliamperage, or shorter exposure time (Fig. 3).

The first phase of our experiment was concerned, therefore, with a modification of the original technique and dealt principally with the factor of contrast, although increased focal spot-screen distance, smaller focal spot tubes, and lessened kilovoltage were utilized in connection with the higher milliamperage ranges. A report of this study was furnished the Committee on Standardization of X-ray Technique and Apparatus, American Sanatorium Association, and may be here summarized:[6]

Apparatus used—Rotating anode line focus tube with 2 mm. focal spot (GE RT 1–2); fluoroscopic screen, Type B; Leica camera, lens 1.5 F; Eastman Super-X film, 35 mm.

Calibration (patient)—20B cm.

Technique—Roentgen-ray tube voltage (variable factor). Focal spot-screen distance—0.92 meter. Screen-film distance—1.06 meters. Roentgen tube current—50, 100, 200, 300, 400 ma. Milliampere-seconds—7.5, 20, 40, 60, 80. Exposure time—0.2 sec. Developing time—22 min., using D-76 Eastman developer.

*Conclusions:* Increased contrast, just as with non-roentgenoscopic methods, was noted with ascending milliamperages. Apparatus having transformer ranges of 200 to 400 ma. are suitable for techniques calling for the photographic filming of roentgenoscopic chest images. All films were viewed through the negatoscope which served to furnish 2 d enlargement.

It will be noted that the developing time for fine grain developer is excessive, that is, twenty-two minutes, when contrasted with the three and a half to four and a half minutes of developing time possible with some of the newer developers. Since these films do not require excessive enlargement, ordinary developing solutions, utilizing the time and temperature factors common to roentgen films, were proved to be entirely satisfactory. All films, however, were developed in total darkness. It was found that Ultra-Speed Panchromatic film was definitely faster and offers greater contrast than either Super-X or Super-XX. Since ordinary Dupli-tized roentgen film requires the use of undetermined special fluoroscopic screens, there would seem to be every advantage in utilizing photographic films of 35 mm. size which are commercially available and may be processed exactly in the same manner as roentgen film. Thus it has been possible to modify de Abreu's technique by adding contrast through selection of film, developer and the utilization of higher milliamperages (see Fig. 3). The effective range for chest films varied from 60 to 90 kv. (peak) at 300 ma., 48 inch distance, and 0.2 sec. exposure time.

Five hundred milliampere techniques were possible at 0.1 sec., at 36 inch distance for all chest calibrations, and at 48 inch distance for the smaller chests.

Our modified technique requires: Apparatus used—Rotating anode line focus tube with 2 mm. focal spot (GE RT 1–2); fluoroscopic screen, Type B; Leica camera, 1.5 F; Agfa Ultra-Speed Panchromatic film 35 mm.; roentgen tube variable; roentgen tube current, 100 to 500 ma.; exposure time, 0.1, 0.2 sec.; developing time 4½ min.; 65° F., Kodalk developer.

This group of films was viewed with the Leitz 35 mm. projector (enlargement approximately 5–6 d) which provides sharp-imaged projections upon heavily glazed white paper of 9×11 cm. size and which we consider diagnostically superior to the 2 d enlargements by the de Abreu negatoscope. It is felt that these films should not be too greatly enlarged and that the method is sufficiently diagnostic to suggest the need for direct roentgenography wherever abnormal densities are encountered. One can reasonably conclude that the method is definitely superior to roentgenoscopy by reason of the permanence of record, higher contrast, and opportunity for more deliberate interpretation. Obviously, the cost of films utilizing this technique is a matter of a few cents for each exposure but the method should be employed only where surveys could not otherwise be made or where roentgenoscopy is being used in place of roentgenograms for economic reasons.

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# ABSTRACTS OF ROENTGEN AND RADIUM LITERATURE

## ROENTGEN DIAGNOSIS

### NECK AND CHEST

Lazeanu, E. Le diagnostic radiologique des lésions de l'artère pulmonaire. (The roentgenologic diagnosis of lesions of the pulmonary artery.) *J. de radiol. et d'électrol.*, Feb., 1938, *22*, 49–59.

Roentgenologically, lesions of the pulmonary artery are indicated by dilatation, hyperpulsation and increase in density. These findings may be due to changes in the wall of the artery or to hypertension in the lesser circulation.

Primary atheroma of the pulmonary artery is associated with bouts of dyspnea and cyanosis, often without cardiac failure. Hemoptysis is frequent. Roentgenologically, there is dilatation of the artery, accentuation of the hilar shadows and increase in the size of the right heart. Syphilis is thought to be a common cause but other etiological conditions have been described.

Aneurysm of the pulmonary artery is relatively rare. One case manifested intense dyspnea, cyanosis and edema of the lower limbs. The liver was tender to pressure. Roentgenologically there was a prominence of the pulmonary artery segment. The heart was enlarged and left ventricular hypertrophy was present. The appearance of the lung suggested venous stasis. In the right oblique position, an aneurysmal dilatation of the pulmonary artery was seen with well-defined pulsations.

Insufficiency of the pulmonary artery is shown roentgenologically by a prominence of the middle arc in its upper portion with increased pulsations. Pezzi described a "hilar dance." Clinically there is a diastolic murmur at the 2nd left interspace propagated along the left border of the sternum.

Stenosis of the pulmonary artery is rare and not compatible with long life. The roentgen appearance is that of the "coeur en sabot." In 90 per cent of the cases there is also dilatation of the pulmonary artery.

Changes in the pulmonary artery in patients with mitral stenosis show either an arteritis or a functional insufficiency. When arteritis is present, the clinical picture of the mitral stenosis is modified by two important clinical signs—dyspnea on effort rapidly becoming permanent and exaggeration of the cyanosis of the lips, mucous membranes and extremities. Hemoptysis is frequent and episodes of suffocation occur. Roentgenologically, there is dilatation of the pulmonary artery and the hilar shadows as well as evidence of venous stasis. Functional insufficiency of the artery is not unusual. The heart shows a mitral configuration, the pulmonary artery is dilated and pulsation is marked.

Persistence of the arterial canal, arteriovenous aneurysm and cardiac insufficiency may show pulmonary artery dilatation.

Pezzi called attention to hypertension of the lesser circuit in some cases of systemic hypertension and said that the condition favored the appearance of episodes of acute pulmonary

edema. The patients are subject to pulmonary apoplexy, infarct and thrombosis of the pulmonary vessels.

In chronic pulmonary diseases like emphysema, fibroid, phthisis, etc., sclerosis of the pulmonary artery may be found. The changes occur slowly in the artery and may ultimately give rise to progressive and permanent cyanosis. Dilatation of the artery is found with accentuation of the hilar shadows and right heart enlargement.—*M. L. Sussman.*

COGGIN, CHARLES B., GRIGGS, DONALD E., and STILSON, WALTER L. The heart in pneumoconiosis. *Am. Heart J.*, 1938, *16*, 411–421.

The authors have studied 205 cases of pneumoconiosis from the records of the Los Angeles County Hospital to determine the incidence and character of associated heart disease. In the group were 102 cases with autopsy study. The disease was regarded as advanced in 55 cases and as far advanced in 146. The patients were men for the most part in the sixth and seventh decades. The cardiac rhythm was usually regular; auricular fibrillation was present in only 6 cases. The serological tests indicated syphilis in 20 per cent of the patients studied and this is about three times the average hospital incidence. Marked cyanosis was present in 27 patients, but polycythemia was rare and anemia fairly common (below 4 million per cubic millimeter in 18.5 per cent). Right axis deviation was found in 37 per cent of the 43 cases in which electrocardiographic studies were made.

Definite congestive heart failure with edema, hepatic enlargement, or ascites occurred in about 50 per cent of the patients who died and in 10 per cent of the living patients. About 40 per cent of the cases studied post mortem showed an active tuberculosis.

Roentgenograms of the chest were available for study in 105 cases. In some cases the pulmonary changes were so marked as to preclude estimation of the heart size. Definite cardiac enlargement was recognized in 25 per cent of the cases, but in only 5 per cent was it thought to be right ventricular. A much higher incidence of right ventricular enlargement was found at autopsy. In many cases the region of the pulmonary conus was observed by the parenchymal changes, but in 22 per cent of the entire group the pulmonary conus was definitely enlarged. The authors believe right ventricular hypertrophy may be present to a considerable degree without giving evidence on the posteroanterior silhouette. Enlargement of the right auricle which constitutes the right border of the heart is a late sign and of little practical value. The measurement of the transverse diameter of the heart and the cardiothoracic ratio also proved of little value, and these were above the maximum normal in only 7.7 per cent of the cases. The basal or broad diameter appeared to be more sensitive and exceeded the normal in 47.5 per cent.

Of the 102 autopsy cases, 29 showed evidence of organic heart disease other than cor pulmonale. The estimation of relative ventricular hypertrophy was made from the thickness of the ventricular walls. Excluding the patients with organic heart disease, hypertrophy of the right ventricle was found in 52 per cent of the cases and hypertrophy of both ventricles in 62 per cent. In two-thirds of the cases the heart weighed more than 350 grams. Hearts weighing over 500 grams occurred most often in patients with organic heart disease other than cor pulmonale.

The clinical diagnosis of cor pulmonale in pneumoconiosis is suggested by accentuation of the pulmonary second sound, marked cyanosis, right axis deviation in the electrocardiogram, and a prominence of the pulmonary conus and increase in the basal diameter of the heart in the roentgenogram. The onset of heart failure is a terminal event and with tuberculosis the most common cause of death.—*W. A. Evans, Jr.*

UNGERLEIDER, HARRY E., and CLARK, CHARLES P. A study of the transverse diameter of the heart silhouette with prediction table based on the teleoroentgenogram. *Am. Heart J.*, Jan., 1939, *17*, 92–102.

The authors have modified the formula of Hodges and Eyster in predicting the transverse diameter of the heart measured on teleroentgenograms. The study is based on a height-weight index, $\frac{w \times 10}{h}$, and the transverse diameter of the heart, T.D., as measured in 1,460 subjects. The curve obtained in plotting these values was a parabola. For this reason a calculation was made of $\frac{w(\text{lb.}) \times 100{,}000}{h(\text{in.})(d)^2(\text{mm.})}$, $d$ being the transverse diameter of the heart, and a constant of 13.83 was obtained. With this constant a table has been drawn up giving the

predicted T.D. for any given height and weight. It was found that no significant correction was necessary for age even for those over fifty. Variations in blood pressure up to 140 mm. produced no significant effect. Increases over this value were associated with progressive increase in the actual cardiac diameter over the predicted figure. A curve is constructed giving the distribution of deviations by per cent of actual from theoretical diameters. The authors have considered for purposes of life insurance selection that any heart diameter more than 10 per cent greater than the average is indicative of cardiac hypertrophy. We note, however, that a considerable number of cases fall in the ±20 per cent range and some are found out to ±30 per cent and beyond.—*W. A. Evans, Jr.*

GOTTA, HÉCTOR. Size and shape of the heart in hyperthyroidism; a teleroentgenographic study of two hundred cases. *Arch. Int. Med.*, June, 1938, *61*, 860–874.

Some observers mention such an entity as "thyroid heart." There is much contradictory evidence, in this regard, along pathologic-anatomic, electrocardiographic and roentgenographic grounds. The author has therefore analyzed 200 cases of hyperthyroidism on the basis of clinical, electrocardiographic and teleroentgenographic studies. Repetitions of these studies were accomplished with 86 of these cases. Of these, 74 had achieved recovery whereas 12 continued to manifest evidence of hyperthyroidism. Posteroanterior roentgenograms were obtained, using 2 m. focal-film distance and exposure times of 1/10 second. Measurements were made as to the internal diameter of the thorax and the long and transverse diameters of the heart and notations were recorded as to abnormalities of configuration. The cases were then classified according to the author's opinion of "normal," "slightly enlarged," "appreciably enlarged" or "greatly enlarged"—in order to take into account individual constitutional variations and avoid dependence upon abstract criteria such as the cardiothoracic index or tables of standard values. On this basis, 80 cases were classified as normal; 64, as slightly enlarged; 30, as appreciably enlarged and 26 as greatly enlarged. The incidence of enlargement of the cardiac area was found to increase with age and with the duration and intensity of the hyperthyroidism. The greatest number of those, showing enlargement, were found to have, besides their hyperthyroidism, other cardiac bases for enlargement, such as arteriosclerotic heart disease, hypertension, rheumatism, renal disease, etc. In fact, only 27 per cent of the cases of enlargement were finally attributed to the hyperthyroid condition *per se*. Interval studies of 12 cases revealed practically no change in the cardiac dimensions, even though the hyperthyroid state continued. In more than half of the patients studied, after recovery from hyperthyroidism, there was no modification of the cardiac area; a decrease in the cardiac area was found in less than one-seventh of these patients (almost all of this last group showed hyperthyroidism with cardiovascular disease).

In general, the author believes that hyperthyroidism *per se* brings about slight or no increase of the cardiac area. He acknowledges two defects in his studies: the use of only one plane of roentgenographic projection and the failure of such a method to visualize less than 10 per cent dimension changes.—*A. A. de Lorimier.*